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THE AMERICAN REVIEW OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

OFFICIAL JOURNAL OF AMERICAN THORACIC SOCIETY
MEDICAL SECTION OF THE NATIONAL TUBERCULOSIS ASSOCIATION

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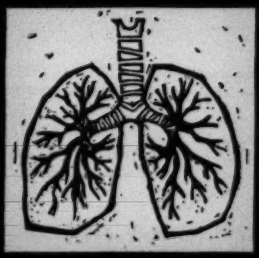

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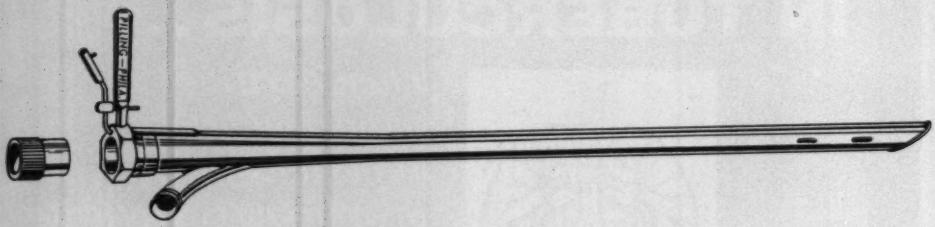

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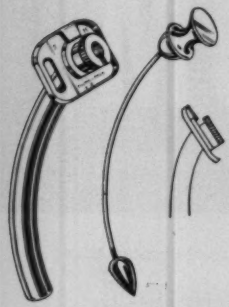

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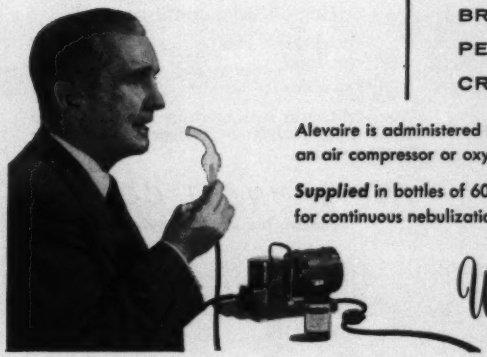

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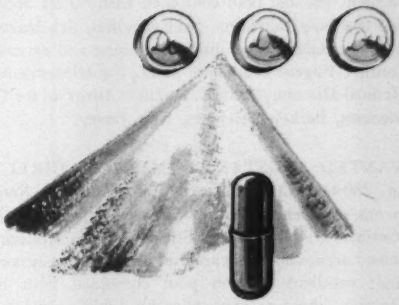

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ERRATUM

The Abstracts section of the May, 1960, REVIEW contained an error on page 803. The last abstract is not taken from the article "Survival and Multiplication of BCG and *M. Tuberculosis* in Mice as Related to Time: A Method of Determination" (in French), by M. Panisset and J. C. Benoit (*Rev Tuberc (Par)*), October, 1959, 97: 437–465), but is an abstract of the article, **The Mouse as a Diagnostic Animal for Differentiation of Strains of Tubercle Bacilli Which are Avirulent or Attenuated in Virulence for the Guinea Pig (BCG Strains, "Atypical" Strains, and Isoniazid-resistant Strains)** by MME F. GRUMBACH*, which was published in *Ann Inst Pasteur (Par)*, 1959, 97: 453–465 (*Institut Pasteur, Paris, France).

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES
Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

VOLUME 82 *August 1960* NUMBER 2

STUDIES ON THE METABOLISM OF ISONIAZID[1, 2, 3]

II. The Influence of Para-Aminosalicylic Acid on the Metabolism of Isoniazid by Man

JOHN H. PETERS

With the technical assistance of R. Larsen and A. Tabri

(Received for publication March 22, 1960)

Introduction

Considerable attention has been given recently to the effects of para-aminosalicylic acid (PAS) on the concentration of isoniazid in plasma or serum. This interest stemmed from the findings that isoniazid is extensively metabolized in man to derivatives with little or no antimycobacterial activity; that acetyl-isoniazid is one of the major metabolic products; and that different human subjects vary substantially in their capacities to form this acetyl derivative (1, 2). These findings led to the cautious suggestion that there might be an inverse relation between the extent to which isoniazid is acetylated and the therapeutic efficacy of this drug (2). Subsequently it was observed (3) that the disappearance of isoniazid from an *in vitro* acetylating system was retarded by PAS. This observation was followed by the demonstration that the concentrations of isoniazid in the plasma of rabbits receiving this hydrazide were increased by the concomitant administration of PAS (3). This latter finding was interpreted as indicating that the adjunctive drug inhibits acetylation of isoniazid *in vivo*, and led to the suggestion that part of the benefit of combination therapy with these agents in human tuberculosis rests on this phenomenon. This concept has been pursued by a number of investigators (4–6) who have presented data which indicate that the simultaneous administration of PAS effected a two- to threefold increase in the concentration of isoniazid in the serum of some tuberculous patients.

In the above clinical studies, the concentrations of isoniazid were measured microbiologically with methods possessing rather large inherent errors and questionable specificity. Moreover, determinations were made at isolated and arbitrarily selected times during absorption. No attempts were made to evaluate the effects of PAS on either absorption or total metabolism of isoniazid. Recognition of these deficiencies was in part responsible for the development of highly specific and sensitive procedures for measuring the concentrations of isoniazid in blood plasma (serum) and urine in the presence of substantial concentrations of PAS (7). These procedures have been applied to a limited study in a group of normal human volunteers of the effects of PAS on the concentrations of isoniazid and total hydrazides in plasma and on the elimination of this drug and its metabolites in the urine. The results of this investigation are summarized here.

Methods

This report deals with two separate studies of the influence of PAS on the metabolic fate of isoniazid. The first, carried out on 4 subjects, was concerned only with the urinary elimination of isoniazid and its total metabolites (isonicotinic acid derivatives). The second study, performed subsequent to the development of the fluorometric method for determining isoniazid in plasma (7), involved measurements of both the plasma concentrations of this compound and its hydrazide metabolites and the urinary output of these moieties

[1] From the Christ Hospital Institute of Medical Research, Cincinnati, Ohio.

[2] Preliminary accounts of these studies have been presented at the Seventeenth and Eighteenth Conferences on the Chemotherapy of Tuberculosis, Veterans Administration–Armed Forces, 1958, 1959.

[3] This investigation was supported in part by research grant E-509 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

in a group of 9 normal subjects, 4 of whom had participated in the initial study.[4]

In the first experiment, 5 mg. per kg. doses of isoniazid,[5] dissolved in 250 ml. of water, were administered at 8:00 a.m. on each of three successive days. On the second and third days, 12 gm. doses of PAS[6] were also administered, 4 gm. at the time of ingestion of isoniazid and 4 gm. eight and sixteen hours later. To ensure sufficient urine volumes, 250 ml. of water were also ingested at one, eight, and sixteen hours. Urine was collected on each of the treatment days at one, two, four, eight, sixteen, and twenty-four hours after ingestion of isoniazid. In addition, for control purposes, urine was collected in the same manner when the subjects received no drugs or only PAS. All urines were stored at 5°C. under toluene prior to analysis.

In the second study, plasma was obtained as described previously (7) one, two, four, and eight hours after administration, and urine was collected fractionally as described above. One week separated the single- and double-drug study. The conditions of administration of drugs were the same as in the first study.

Determination of isoniazid in urine: Measurement of isoniazid in urine of subjects receiving this drug and PAS made it necessary to devise a procedure for separating gamma quantities of the hydrazide from milligram quantities of the companion compound. This was accomplished by employing a column of a strongly basic ion-exchange resin, Amberlite® IRA-400. By virtue of their acidic properties, PAS and its metabolites are absorbed by the resin, whereas the neutral unionized isoniazid is not. With this technique, 10 γ of isoniazid can easily be separated from as much as 6,000 γ of PAS.

In the first study, following removal of PAS and its derivatives, isoniazid was measured with a modification of the Short procedure (9). One milliliter of urine was diluted with 1 ml. of water in a 5-ml. beaker and the pH was adjusted to 7–8 (glass electrode) with a dilute sodium hydroxide solution. The diluted urine was added to a column of the resin,[7] the effluent liquid being collected in a 10-ml. volumetric flask. The contents of the flask were adjusted to volume by rinsing the electrodes and beaker with distilled water and passing the rinse water through the column. For assay of isoniazid content, 7 ml. of the effluent liquid were treated with 2 ml. of a 0.5 M phosphate buffer, pH 6.65 ± 0.5, and 1 ml. of a freshly prepared aqueous solution of sodium 1,2-naphthoquinone-4-sulfonate (1 mg. per ml.). The resulting color was allowed to develop one hour in the dark and was read with minimal exposure to light on a Klett-Summerson colorimeter equipped with a No. 44 filter. In this procedure, neither acetylisoniazid nor isonicotinic acid contribute to the color formed, and the recovery of 10 to 60 γ of isoniazid added to control urine or urine from subjects receiving PAS was 94 ± 2 per cent. However, negative urine blanks, i.e., samples from control urine giving colorimeter readings lower than the reagent blank, were frequently observed. This was compensated for by diluting the respective fractional control and treatment urine collections to the same volume. Thereby, the control urine blank could be subtracted directly from its corresponding treatment sample and the total milligrams of isoniazid contained in the treatment sample could be obtained by calculation. Assays were performed in duplicate which varied by no more than 2 per cent from their mean.

In the second study, this procedure was simplified and the reaction with vanillin (10) was used to determine isoniazid content. Urine (1 ml.) was mixed with 1 ml. of 0.5 M phosphate buffer, pH 7.00 ± 0.05, added to the resin column[7] and the effluent liquid was collected in a 10-ml. graduated test tube. The tube which originally contained the buffered urine and the resin column were rinsed twice with 2 ml. of distilled water. After adjusting the combined effluent liquid volumes to 6 ml. with distilled water, 1 ml. of N hydrochloric acid was added. To obtain a blank value, the acidified solution was then read in a 1 cm.[2] cuvette against a reagent blank at 365 mμ on the Beckman DU spectrophotometer. The solution was returned to its collection tube and treated with 1 ml. of a 2 per cent vanillin[8] solution in 25 per cent ethanol, mixed, and reread, in the same cuvette at 365 mμ against a similarly treated reagent blank.

The optical density was determined within ten

[4] All of the volunteers were normal males. Their ages ranged from twenty-two to forty-nine years; their weights from 67.6 to 96.8 kg. None were receiving other medications during the studies.

[5] Purified as previously described (7).

[6] Sodium *p*-aminosalicylate dihydrate (Hellwig) was used. A sample of this material was dried at 105°C. to constant weight. The observed weight loss was 16.9 per cent (theory requires 17.0 per cent). An observed molecular extinction coefficient of 12,400 at 265 mμ in phosphate buffer, pH 7 (8), indicated a purity of 95 per cent.

[7] The chloride form of Amberlite IRA-400 (Rohm and Haas) was pretreated by stirring in excess 2 N hydrochloric acid and exhaustively washed with boiled distilled water until the wash liquid was neutral. Columns (diameter 0.5 cm., length 15 cm.) were made by cutting 10-ml. volumetric pipettes 15 cm. below and 3 cm. above the lower end of the bulb area. The upper large diameter area was then flared slightly to facilitate addition of the sample, and the lower end was firepolished until an orifice approximately 1 mm. in diameter was obtained. A small plug of glass wool was tamped into the bottom of the column which was then charged by adding an aqueous suspension of the ion-exchange resin. Packing was effected by gently tapping on the sides of the column with a glass rod. A small plug of glass wool placed at the top of the resin bed provided sufficient surface area to hold the liquid above the resin and thereby prevented the column from "running dry." The resin was discarded after use.

[8] Vanillin (Eastman) was recrystallized from water. The melting point of the purified material was 81–82°C.

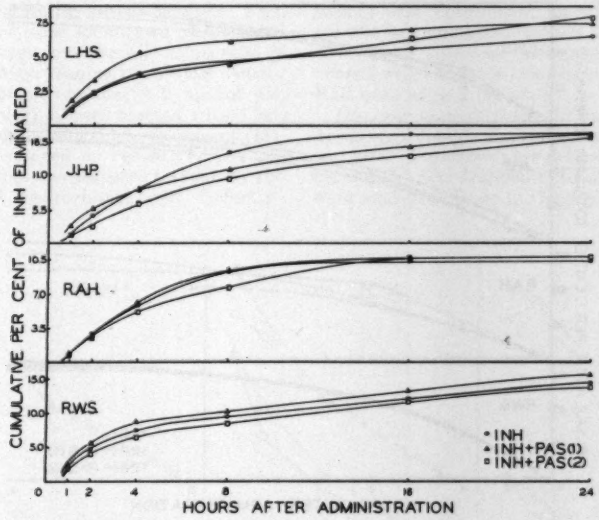

FIG. 1. The urinary elimination of isoniazid (INH) by adult males receiving isoniazid (5 mg. per kg.) alone and in combination with PAS as described in the text.

minutes after addition of the vanillin solution. Subtraction of the optical density of the sample containing no vanillin from that containing this reagent gave a net value due to vanillin-reacting materials. In this way each urinary assay sample served as its own blank. Samples of control urines or urine from subjects taking only PAS gave optical densities in this procedure due to vanillin-reacting materials that were equivalent to less than 1 γ of isoniazid per ml. of urine. Acetylisoniazid was not decomposed to isoniazid by the resin, passed through the columns unchanged, and did not contribute to the vanillin color. The region of linearity in the method was between 1 and 20 γ of isoniazid. As a consequence, urine containing more than 20 γ per ml. was diluted appropriately. Recoveries of isoniazid (2 to 20 γ) added to water, control urine, urine from subjects receiving PAS, or urine from such subjects diluted 1 to 10 with distilled water were the same and equal to 90 $\pm$ 2 per cent. The total net milligrams of isoniazid excreted were obtained by subtracting the total milligrams of isoniazid equivalents of the control fractions from the total milligrams of isoniazid found in the corresponding treatment fractions. Results are expressed as the per cent of the administered isoniazid and are the averages of duplicate determinations which varied by no more than 2 per cent from their mean.

Since, in this procedure, each sample serves as its own blank and since the materials that contribute to the color developed on reaction with vanillin are so low in nontreatment or PAS-treatment urine, the collection of control urine may be dispensed with in work requiring less than maximal accuracy.

Determination of total isonicotinic acid derivatives in urine: The measurement of the elimination of total isoniazid metabolites was accomplished by acid hydrolysis of urinary aliquots and the subsequent determination of the isonicotinic acid produced (11). Urine aliquots were diluted one to one with distilled water, and 1 ml. of this solution was treated with 5 ml. of 6 N hydrochloric acid. Hydrolysis was accomplished by heating the acidified, diluted urine in a sealed ampoule at 120°C. for three hours. One-milliliter aliquots of the hydrolysates were neutralized with 2 ml. of 2.5 N sodium hydroxide, buffered by the addition of 2 ml. of an ammoniacal buffer, pH 8.3 (12), cooled to 0–5°C., and treated with 5 ml. of ice-cold 3.3 per cent aqueous cyanogen bromide solution[9] (fume hood). The samples were read at the time of maximal color development, usually about eight minutes after mixing, on a Klett-Summerson colorimeter using a No. 42 filter. Occasionally a fine black precipitate resulted on cooling the hydrolysates. This could easily be separated by centrifugation at 1,500 r.p.m. for ten minutes.

To correct for color usually obtained in the hydrolysates, internal blanks were determined by treating neutralized and buffered aliquots of the hydrolysates with 5 ml. of distilled water instead of with the cyanogen bromide solution. These samples were read on the colorimeter against a

[9] A stock 10 per cent aqueous cyanogen bromide (Eastman) solution was prepared (fume hood) and stored at 5°C. Just before use, 1 volume of this solution was diluted with 2 volumes of cold distilled water.

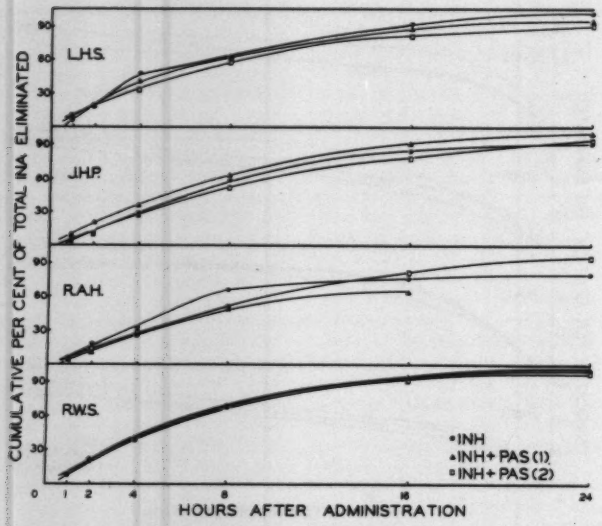

FIG. 2. The urinary elimination of total isonicotinic acid derivatives (INA) by adult males receiving isoniazid (INH) (5 mg. per kg.) alone and in combination with PAS as described in the text.

similarly treated reagent blank. The internal blank values were then subtracted from colorimeter readings obtained on corresponding aliquots of the hydrolysates which were treated with cyanogen bromide to give corrected values. The method is easily sensitive to 0.1 γ of isonicotinic acid per ml. of assay sample which corresponds to 12 γ per ml. of urine. Conformity to the Bouguer-Beer law was observed between 0.1 and 2 γ of isonicotinic acid per ml. of assay sample. As a consequence, urine specimens containing more than 240 γ per ml. after hydrolysis were diluted appropriately. Para-aminosalicylic acid or urine from subjects receiving 12 gm. of this drug per day did not interfere with or contribute to this color reaction. Recoveries of 100 to 200 γ of isonicotinic acid from twenty-four-hour control urines and twenty-four-hour PAS urines were 101 $\pm$ 1 per cent. Isoniazid, acetyl-isoniazid, and isonicotinyl glycine were quantitatively hydrolyzed to isonicotinic acid in this procedure. All values reported were averages of duplicate determinations which agreed within $\pm$3 per cent.

Determination of total hydrazides in urine: These moieties, which are the sum of isoniazid, acid-labile isoniazid derivatives, and acetyl-isoniazid, were measured by application of a procedure which combined slight simplifications of the extraction method used previously (7) with the technique of Maher and associates (13) to measure isoniazid[10] and total hydrazides consecutively in the same sample. One milliliter of urine and 2 ml. of water were added to a 25- by 150-mm. screw-cap (Teflon liner) culture tube containing 3.2 gm. of ammonium sulfate. Following the addition of 1 ml. of 0.1 N sodium hydroxide solution and 30 ml. of a 3:7 i-amyl alcohol-ethylene dichloride mixture,[11] the tube was shaken in a horizontal position for thirty minutes and centrifuged for fifteen minutes at 1,500 r.p.m. Twenty milliliters of the solvent extract were transferred to another culture tube containing 4 ml. of 0.1 N hydrochloric acid solution. After shaking for fifteen minutes and cen-

TABLE 1

INFLUENCE OF PARA-AMINOSALICYLIC ACID (PAS) ON THE PROPORTION OF TOTAL ISONICOTINIC ACID DERIVATIVES EXCRETED AS ISONIAZID DURING 24 HOURS

Subject	Per Cent of Total Isonicotinic Acid Derivatives as Isoniazid*		
	After Isoniazid	After Isoniazid + PAS (Day 1)	After Isoniazid + PAS (Day 2)
L. H. S.	6.5	7.8	8.7
R. A. H.	12.9	16.5	11.6
R. W. S.	14.3	15.4	14.2
J. H. P.	19.6	17.4	18.9

* Calculated from the 24-hour excretion values of figures 1 and 2.

[10] The values for isoniazid obtained by this technique are included in a subsequent communication (14).

[11] The solvents were purified as previously described (7) except that the i-amyl alcohol was not distilled.

trifugation at 1,500 r.p.m. for ten minutes, 3 ml. of the acid extract were withdrawn and treated with 0.2 ml. of a 2 per cent vanillin[8] solution in 25 per cent ethanol. After reading the optical density to determine isoniazid content,[10] 2 ml. of the vanillin-treated solution were reacted with 1 ml. of the *p*-dimethylaminobenzaldehyde reagent (13). The color was developed as before (7) and the volume of the sample was adjusted to 5 ml. by the addition of 0.1 N hydrochloric acid. Color intensity was determined on a Klett-Summerson colorimeter equipped with a No. 44 filter. Recoveries of isoniazid and acetyl-isoniazid from control urine or urine from subjects receiving only PAS were 95 ± 2 per cent.

Determination of isoniazid and total hydrazides in plasma: The plasma concentrations of isoniazid and total hydrazides were determined as described previously (7). Duplicate 3-ml. plasma samples were analyzed. Prior to the experimental studies,

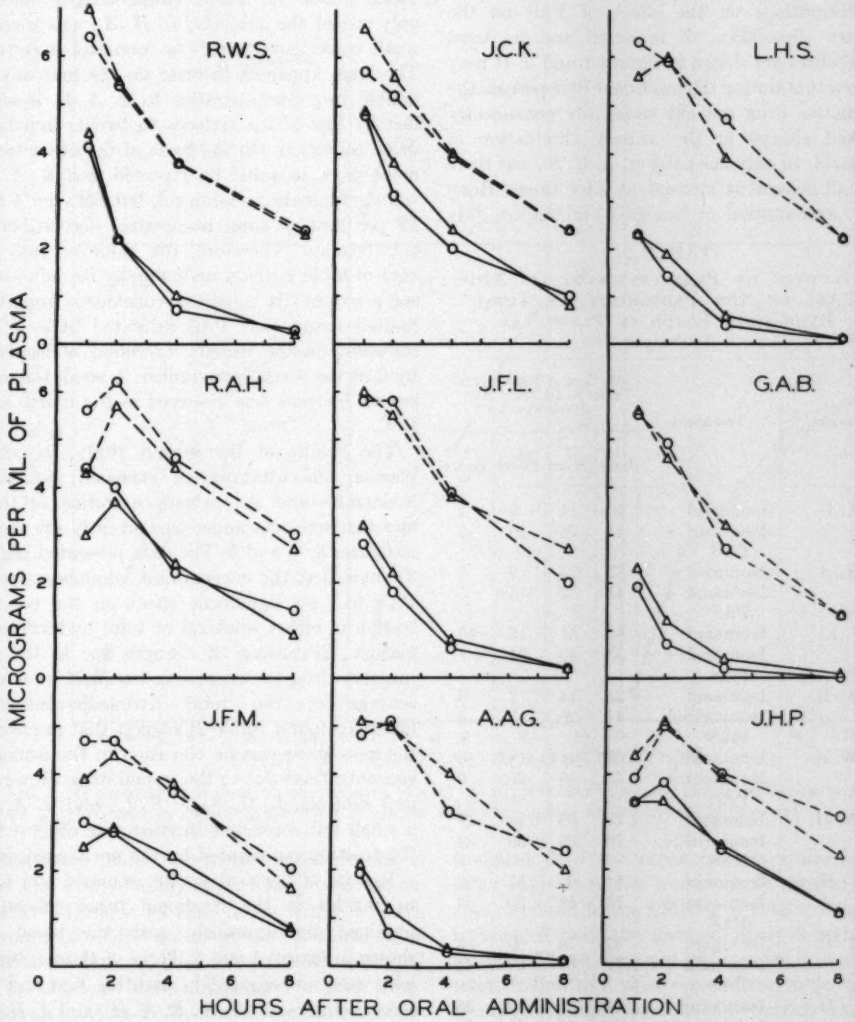

FIG. 3. The plasma concentrations of isoniazid (solid lines) and total hydrazides (broken lines) in adult males receiving isoniazid (5 mg. per kg.) alone (circles) and in combination with 12 gm. of PAS (triangles) as described in the text.

it was determined that PAS or its metabolites did not interfere in the chemical procedures for isoniazid or total hydrazides. Thus, plasma obtained one, two, four, and eight hours following ingestion of 4 gm. of PAS did not show increases in blank values over control plasma. Recoveries of isoniazid from this plasma were the same as from control plasma. As in the previous report (7), total hydrazides are reported as isoniazid equivalents.

Results

Observations on the effect of PAS on the urinary elimination of isoniazid and its total metabolites are shown in figures 1 and 2. It may be seen that during the fractional time periods the adjunctive drug did not cause any consistently marked change in the urinary elimination of isoniazid. In only one subject, *L. H. S.*, was there a small consistent increase at later times. However, examination of isoniazid elimination data alone is not sufficient for evaluation, since PAS may have some influence on the absorption or rate of elimination of the primary drug. The graphs of figure 2 suggest that the second drug was not causing large changes in these parameters. Nevertheless, to compensate for small differences in such factors, the data have been calculated in terms of the per cent of the total isonicotinic acid derivatives eliminated as isoniazid (table 1). These values suggest that in only one of the subjects, *L. H. S.*, was there a small consistent increase in isoniazid excretion. The large apparent increase on the first day of double-drug administration to *R. A. H.* is nullified by loss of the sixteen- to twenty-four-hour urine collection. On the basis of the other treatment days, it would be expected that *R. A. H.* would eliminate no isoniazid, but between 4 and 12 per cent of total isonicotinic derivatives in this fraction. Therefore, the value of 16.5 per cent of table 1 would undoubtedly be reduced to some extent. It must be concluded from this limited study that PAS exhibited little or no influence on the urinary excretion of isoniazid by 3 of the 4 subjects studied. A small but consistent increase was observed in the fourth subject.

TABLE 2

Influence of Para-Aminosalicylic Acid (PAS) on the Proportion of Total Hydrazides Found in Plasma as Isoniazid

Subject	Treatment	Per Cent of Total Hydrazides as Isoniazid after Administration*			
		1 Hour	2 Hours	4 Hours	8 Hours
A. A. G.	Isoniazid	40	14	9	4
	Isoniazid + PAS	41	24	10	5
L. H. S.	Isoniazid	37	24	9	5
	Isoniazid + PAS	41	32	15	5
J. F. L.	Isoniazid	48	31	15	10
	Isoniazid + PAS	53	40	21	7
G. A. B.	Isoniazid	35	14	7	0
	Isoniazid + PAS	41	26	13	4
R. W. S.	Isoniazid	64	41	18	13
	Isoniazid + PAS	63	40	26	9
R. A. H.	Isoniazid	79	65	48	47
	Isoniazid + PAS	70	65	55	33
J. C. K.	Isoniazid	84	60	57	42
	Isoniazid + PAS	74	68	60	33
J. H. P.	Isoniazid	87	76	60	35
	Isoniazid + PAS	77	67	64	48
J. F. M.	Isoniazid	64	60	53	35
	Isoniazid + PAS	64	66	61	50

* Calculated from the data of figure 3.

The results of the second study, in which plasma concentrations of isoniazid and total hydrazides and the urinary excretion of these moieties were determined concurrently, are shown in figures 3, 4, and 5. The data presented (figure 3) show that the concomitant administration of PAS had no significant effect on the concentration of either isoniazid or total hydrazides in plasma. Evaluation of changes due to the adjunctive drug by expressing isoniazid as a percentage of the total hydrazide-containing materials found (table 2) suggest that in most of the men there was no elevation in the isoniazid concentrations due to the second drug. However, in 3 subjects, *L. H. S.*, *J. F. L.*, and *G. A. B.*, a small but consistent increase was observed in the fraction represented by the unchanged drug.

Results of the analysis for isoniazid and total hydrazides in the fractional urine collections obtained simultaneously with the blood are shown in figures 4 and 5. Three of those subjects who were investigated in both the first and the second studies, *L. H. S.*, *R. A. H.*, and *J. H. P.*, excreted approximately the same amounts in the two studies. One subject, *R. W. S.*, showed a large difference in the two studies. He was re-

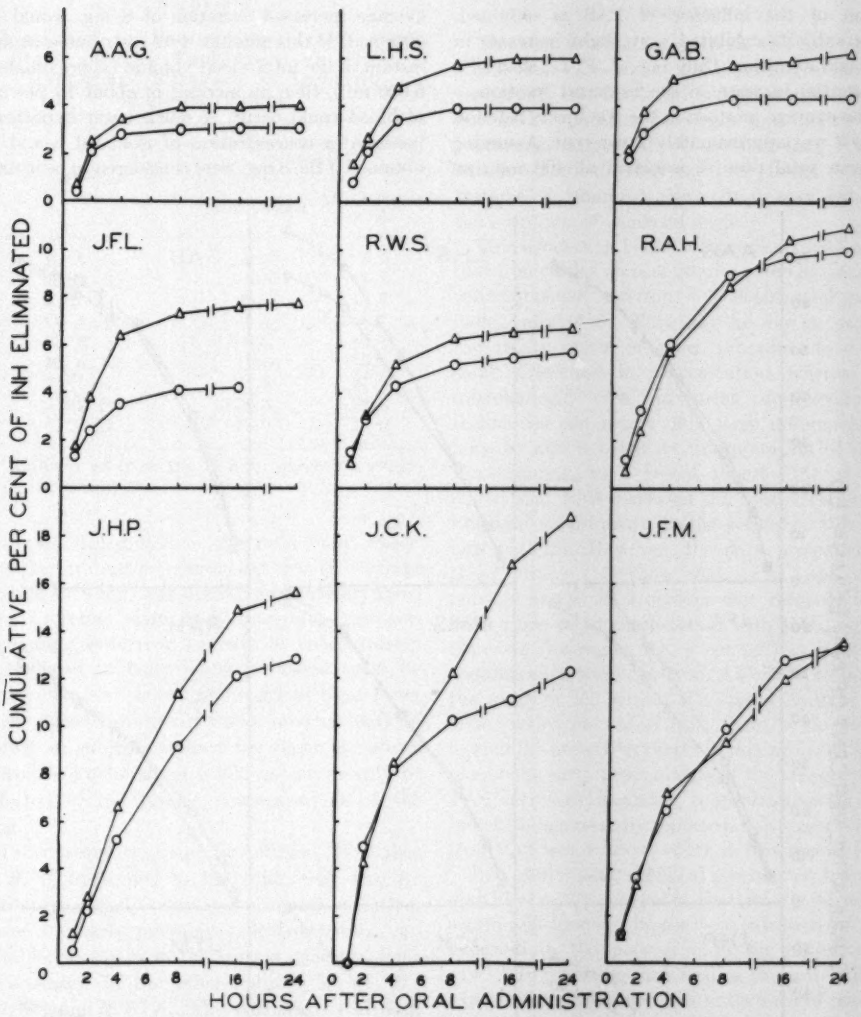

FIG. 4. The urinary elimination of isoniazid (INH) by adult males receiving isoniazid (5 mg. per kg.) alone (circles) and in combination with 12 gm. of PAS (triangles) as described in the text.

investigated under the treatment conditions of the first study, applying the improved ion-exchange technique for assay of isoniazid excreted. Summation of the assays of the fractional urine collections gave 8.0 per cent of the dose excreted in twenty-four hours following isoniazid treatment and 10.8 and 9.4 per cent elimination on the two following days when both drugs were administered. Apparently this subject showed greater variation in extent of metabolism of isoniazid than the other persons studied. The other subjects of the second study showed variable responses to the addition of PAS to the drug regimen if only the data of figure 4 were examined. These apparent differences are mostly relative, however, since some of the subjects also eliminated larger amounts of hydrazide-containing materials. Expressing as before the isoniazid excretion as the percentage of the total hydrazides in the urine (table 3), a more accurate eval-

uation of the influence of PAS is obtained. Most subjects exhibited very slight increases in isoniazid excretion. Only one, *J. F. L.*, showed a substantial increase in the isoniazid fraction.

The average increase in the 9 subjects listed in table 3 was approximately 2 per cent. Assuming a mean total dose of isoniazid at 400 mg., an average increased excretion of 8 mg. would be obtained. If this amount were distributed at any instant in the total blood volume (approximately 6,000 ml.), then an increase of about 1γ per ml. of blood could occur. A much lower hypothetic increase in concentration of isoniazid would be obtained if the 8 mg. were considered to be instan-

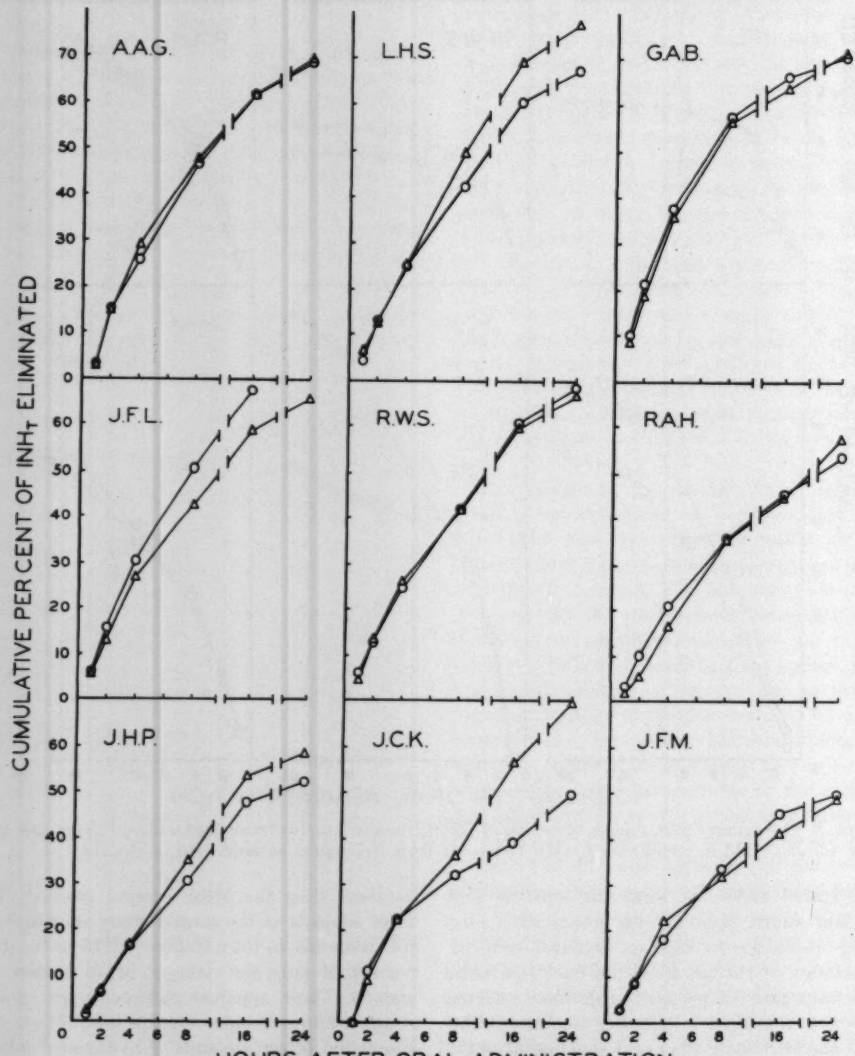

FIG. 5. The urinary elimination of total hydrazides by adult males receiving isoniazid (5 mg. per kg.) alone (circles) and in combination with 12 gm. of PAS (triangles) as described in the text.

TABLE 3

INFLUENCE OF PARA-AMINOSALICYLIC ACID (PAS) ON THE PROPORTION OF TOTAL HYDRAZIDES EXCRETED AS ISONIAZID DURING 24 HOURS

Subject	Per Cent of Total Hydrazides as Isoniazid*	
	After Isoniazid	After Isoniazid + PAS
A. A. G.	4.5	5.5
L. H. S.	5.8	7.7
J. F. L.	6.2	11.7
G. A. B.	6.1	8.7
R. W. S.	8.3	10.1
R. A. H.	18.6	19.1
J. C. K.	24.8	27.2
J. H. P.	24.6	26.6
J. F. M.	26.9	28.0

* Calculated from the 24-hour excretion values of figures 4 and 5.

taneously distributed in the total body water. However, it must be pointed out that the average increase of 8 mg. was derived from twenty-four-hour excretion data and, therefore, any corresponding estimated increase in concentration of isoniazid in body water or blood must be distributed over some finite length of time. From these considerations, it seems obvious that in almost all subjects studied the slight elevations in isoniazid elimination would not necessarily be reflected in the plasma concentrations of the drug.

Taken together, these two studies show that *L. H. S.* responded to the adjunctive drug by exhibiting slightly increased isoniazid excretion. These increases probably reflected barely discernible elevations in the plasma concentrations of isoniazid. In the other subjects, *R. A. H.*, *J. H. P.*, and *R. W. S.*, who participated in both studies, PAS caused either no change or very slight increases in isoniazid excretion and no detectable consistent change in the plasma concentration of the drug. Of the remaining 5 subjects, only 2, *J. F. L.* and *G. A. B.*, responded to the adjunctive drug by exhibiting slightly increased plasma concentrations and urinary excretion of isoniazid. Therefore, the conclusion that PAS had no effect on the metabolism of isoniazid in most persons and, at best, only a slight influence in others seems justified.

DISCUSSION

The results obtained in both the first study, which was carried out on consecutive days of treatment, and the larger second study, wherein one week separated the single- and double-drug treatment, suggest the conclusion that PAS is without marked effect on the plasma concentrations of isoniazid although it may enhance the excretion of isoniazid slightly.

This conclusion is not in agreement with those based on earlier clinical studies wherein isoniazid concentrations in serum were determined microbiologically (4–6). This may be due in part to the ability of the chemical procedure to detect small differences in concentration, whereas the microbiologic tests in using double-dilution techniques can report only large differences. It may be also a result of interpretation of data. For example, in a recent report (15), it was stated that PAS increased the concentrations of isoniazid significantly in the serum of tuberculous patients. However, the data presented by these writers (15) show that, of a total of 14 pairs of assays in 9 persons who received isoniazid alone or in combination with PAS, only 5 increases (averaging 0.8 γ per ml.) in isoniazid concentration were observed. All others remained the same or fell within the stated limit of the assay technique. Moreover, there is no longer unanimity among workers on this problem since one of the early protagonists of the concept that PAS increases isoniazid concentrations in the blood (5) has recently reported, in a larger study, that PAS was without effect in this regard (16).

In a study using chemical procedures, Lauener and Favez (17) concluded that PAS induced "a significant increase in the concentration of free isoniazid in the plasma . . . in the majority of cases." In reporting their results, the writers have expressed the isoniazid concentrations of plasma as a percentage of the total isonicotinic acid derivatives present. In 4 of 26 instances reported (figure 2, *loc. cit.*) the per cent of isoniazid of the total isonicotinic acid derivatives was 100, i.e., isoniazid accounted for all of the isonicotinic acid derivatives present. It must be concluded that in these instances *no* alteration or metabolism of isoniazid had occurred during three hours after administration of the drug. In the limited experience of the present writer, the subject least active in metabolizing isoniazid exhibited a plasma concentration of isoniazid after

two hours which was 76 per cent of the concentration of the total hydrazides (table 2). Moreover, while the total hydrazide concentrations represent the sum of isoniazid and acetyl-isoniazid, the total isonicotinic acid determinations performed by Lauener and Favez would be the summation of these in addition to isonicotinic acid and its conjugates.

Other writers (5, 13, 15) have consistently observed higher concentrations of isoniazid and its derivatives than unchanged drug two hours after administration. Lauener and Favez used the Scott procedure (18) for determining the concentrations of isoniazid in plasma. This technique had been previously evaluated by both Hughes (19), formerly of this laboratory, and the writer. Both investigators, in independent studies, found that the method lacked precision and accuracy. Another laboratory has reported that this method is useful only for measuring quantities greater than 1 to 2 γ of isoniazid per ml. (20).

In conclusion, in the present writer's opinion, the results of the present studies suggest that PAS does not significantly influence the acetylation of isoniazid in humans receiving therapeutic doses of these drugs. This conclusion in no way denies the contribution of PAS to the chemotherapy of tuberculosis when used in combination with isoniazid. This contribution most probably rests on possession of antimicrobial activity independent of that of isoniazid (21, 22).

Summary

The influence of para-aminosalicylic acid (PAS) on the metabolism of isoniazid by man has been investigated. In one study, the urinary excretion of isoniazid and its total metabolites (total isonicotinic acid derivatives) has been determined following administration of isoniazid alone and in combination with PAS. No marked effect of the adjunctive drug was noted. In a second study, the plasma concentrations of isoniazid and total hydrazides and the urinary excretion of these materials were measured simultaneously. Although urinary excretion of unchanged isoniazid was found to be very slightly increased in some of the subjects studied, effects on plasma concentrations of this compound were essentially nonexistent. These findings provide no support for the concept that therapeutic doses of PAS block acetylation or otherwise alter the metabolism of isoniazid in man.

Sumario

Estudios del Metabolismo de la Isoniacida. II. El Influjo del Acido Para-Aminosalicílico sobre et Metabolismo de la Isoniacida por el Hombre

Se ha investigado el influjo del ácido para-aminosalicílico sobre el metabolismo de la isoniacida por el hombre. En un estudio, se determinó la excreción urinaria de isoniacida y sus metabolitos totales (derivados totales del ácido isonicotínico) después de administrar isoniacida, sola y combinada con PAS. No se notó mayor efecto de la droga agregada. En el segundo estudio, midiéronse simultáneamente las concentraciones plasmáticas de isoniacida e hidracidas totales y la excreción urinaria de estas substancias. Aunque se observó que la excreción urinaria de la isoniacida inalterada había aumentado muy levemente en algunos de los sujetos estudiados, los efectos sobre las concentraciones plasmáticas de dicho compuesto fueron en el fondo nulos. No ofrecen estos hallazgos apoyo alguno al concepto de que dosis terapéuticas de PAS impiden la acetilación o alteran en otra forma el metabolismo de la isoniacida en el hombre.

Resume

Etudes sur le metabolisme de l'isoniazide. II. L'influence de l'acide para-amino-salicylique sur le métabolisme de l'isoniazide chez l'homme

L'auteur a étudié l'influence de l'acide para-amino-salicylique (PAS) sur le métabolisme de l'isoniazide chez l'homme. Dans une étude, l'excrétion urinaire d'isoniazide et ses métabolites totaux (dérivés totaux de l'acide isonicotinique) a été déterminée à la suite de la prise d'isoniazide seul et associé à du PAS. On ne nota pas d'effet remarquable du médicament ajouté. Dans une seconde étude, les concentrations, dans le plasma, de l'isoniazide, des hydrazides totaux, et l'excrétion urinaire de ces produits furent simultanément mesurés. Bien que l'excrétion urinaire d'isoniazide non transformé fut trouvée légèrement augmentée chez quelques sujets étudiés, les effets de ce produit sur les concentrations du plasma ne comptent pas. Ces données n'apportent rien pour soutenir la conception que des doses thérapeutiques de PAS bloquent l'acétylation ou modifient d'une autre façon le métabolisme de l'isoniazide chez l'homme.

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THE EFFECTS OF INTERMITTENT POSITIVE PRESSURE BREATHING IN SIMULATED PULMONARY OBSTRUCTION[1, 2, 3]

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INTRODUCTION

Self-cycling mechanical respirators generally are quite effective, and may be lifesaving, in patients who have "restrictive" ventilatory insufficiency due to central nervous depression, muscular paralysis, or lung displacement. In ventilatory failure due to "obstructive" disease this form of therapy often has been of limited value, principally because patients cannot coordinate their inflexible breathing pattern with the different and rigid pattern of automatic machines (1–4). Consequently, demand-type assistors have been thought best suited in these situations.

The effect of various experimental intermittent and continuous positive pressure devices were first compared in normal subjects about fifteen years ago. Continuous positive pressure breathing (CPPB) produced a rise in alveolar oxygen pressure and a drop in cardiac output proportional to the rise in mask pressure; it caused little hyperventilation and furthered passive inspiration and active expiration (5–7). Those intermittent positive pressure breathing (IPPB) devices in which there was a gradual diminution of expiratory pressure ("Type I" curve) produced effects much like continuous positive pressure breathing (5). Those which allowed a rapid return of expiratory pressure to ambient levels ("Type III" curve) induced considerable alveolar hyperventilation with attendant decrease of alveolar carbon dioxide tension but with little change in cardiac output (5, 7, 8). These characteristics implied clinical usefulness which was readily demonstrated in pulmonary insufficiency due to respiratory muscle failure (9, 10).

Beneficial effects of intermittent positive pressure breathing in chronic obstructive emphysema and bronchial asthma appear to be supported by a large number of reports (11–21). Unfortunately, results frequently have been concerned only with symptomatic response; the effect of coincident bronchodilator therapy often has not been separated from that produced by IPPB alone; the degree of ventilatory insufficiency usually was not estimated quantitatively; and, most important, few have studied either the ability of IPPB to increase effective ventilation or the reasons why it has often failed in the most severely ill.

The present writers have observed in detail the effect of intermittent positive pressure breathing in 8 patients with chronic obstructive emphysema hospitalized with severe respiratory acidosis. In 4 of these there was no lowering of arterial carbon dioxide tension during or after IPPB therapy. Also, these 4 responded to IPPB with a decrease of respiratory rate and a slight decrease in external ventilation. This led the writers to suspect that in some way positive pressure therapy may have increased the work of breathing or increased obstruction to expiratory air flow which prevented more effective ventilation.

The basic physiologic defect in chronic obstructive emphysema is an elevated airway resistance which is more marked during expiration (22–27). The operation of a check-valve mechanism has been described, and it has been thought that, during expiration, the tissue pressure surrounding the smallest airways may become greater than that within, causing them to collapse. As stated by Dayman (23), the operation of such a ". . . mechanism is subject to

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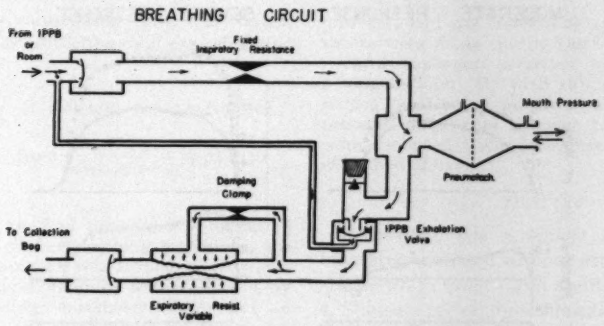


FIG. 1. Experimental breathing circuit.

the interrelated factors of lung tension, pulmonary pressure, rate of airflow and intrinsic disease of the airways, in such a way as to minimize the obstruction in health and render it virtually absolute in certain forms of emphysema." Indeed, it has been shown recently that, for a given state of lung inflation, a maximal expiratory flow rate exists which cannot be exceeded regardless of the pressure applied to the system; and that this maximal flow rate is sharply reduced in emphysema (28).

An attempt was made to investigate the interrelationship of these factors clinically, but it was found that severely and acutely ill patients could neither tolerate prolonged experimental procedures nor maintain the required steady state condition. Therefore, it was decided to mimic the hypothesized faulty mechanics of the respiratory bronchiole and its environment in chronic obstructive disease. A device for external obstruction to air flow was so constructed that by breathing through it normal subjects closely approximated the respiratory pressure-flow pattern of patients with severe emphysema. The present report deals with results of studies using this system. The findings suggest possible reasons why IPPB may fail to benefit certain patients with "obstructive disease."

METHODS

The external breathing circuit, which was used to reproduce the abnormal breathing pattern, is shown in figure 1. The inspiratory side, shown uppermost, included a fixed resistance in the form of a constriction in the tubing. The apparatus dead space volume, to the right, was 230 ml., and consisted of a five-way valve (not shown) with a sampling needle within for continuous carbon dioxide analysis, a pneumotachograph, and a

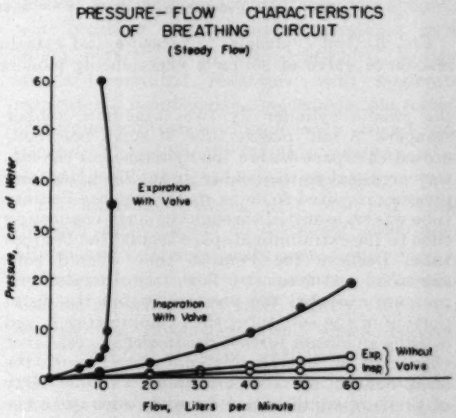


FIG. 2. Pressure-flow characteristics of breathing circuit under steady flow conditions, with and without added resistance.

small-bore tube at right angles for measuring airway pressure. Lowermost is the expiratory circuit with an IPPB exhalation valve assembly modified by the addition of an air-tight metal enclosure around the expiratory vents so that the expired gas could be channeled through a variable resistance valve. Both inspiratory and expiratory circuits were protected by additional one-way "J" valves (figure 1) to prevent reversal of flow regardless of pressures applied. Not shown is a large-bore, three-way aluminum stopcock which was inserted at the end of the expiratory circuit; this cock permitted expired gas collection either in a meteorologic balloon or in a 9-liter spirometer.

The variable expiratory resistance, shown in figure 1, consisted of a 10-cm. segment of a thin-walled, tubular Penrose surgical rubber drain enclosed within a rigid, transparent, plastic cylinder, 5 cm. in diameter. The Penrose tubing bridged an 8-cm. gap between two metal tubes, 2 cm. in diameter, which were fixed air tight within

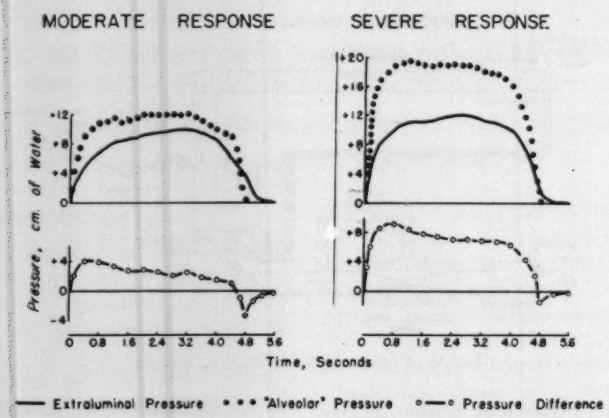


FIG. 3. Oral ("alveolar") pressure and extraluminal pressure during expiration through variable resistance valve of subjects experiencing moderate and severe obstruction.

the plastic cylinder by two large-bore rubber stoppers. A stiff plastic tube of small bore connected the space within the cylinder and the airway proximal to the rubber drain. Thus, the oral pressure required to move air through the Penrose tube was transmitted through the small connecting tube to the extraluminal space around the Penrose tube. Because the Penrose tube offered considerable resistance to flow, the extraluminal pressure exceeded the pressure within the distal portion of the soft tube, thus compressing it and causing an abrupt further rise in airflow resistance (figure 2). A "damping" clamp placed across the small connecting tube permitted a variable delay of pressure equilibration from the airway to the extraluminal space and maintained the extraluminal pressure at a lower level than that in the proximal airway (figure 3).

The steady flow-pressure characteristics of the inspiratory and expiratory circuits are shown in figure 2. During expiration through the artificial resistance an increasing pressure drop at first caused a rapidly increasing expiratory flow to about 10 L. per min. at 4 cm. of water pressure. Thereafter, a maximal flow of 12 L. per min. was achieved with a very large pressure, and this rate of flow could not be exceeded regardless of the pressure applied. On the contrary, with pressures above 35 cm. of water, the rate of flow tended to diminish slightly.

The unsteady flow-pressure gradients between the proximal airway and extraluminal space are shown in figure 3. The collapsible thin-walled tube has been considered as the "respiratory bronchiole"; in this connection the proximal airway or oral pressure was like "alveolar pressure," and the extraluminal pressure was like "intrapleural pressure."

Five normal volunteers were studied fasting, in the supine position. They were allowed to accommodate for twenty minutes while breathing through either the dead space of the apparatus shown in figure 1 but without inspiratory or expiratory added resistance, or the entire resistance circuit of figure 1. Then followed a test period either with or without assistance by a conventional IPPB device[6] set at 17.5 cm. of water pressure. *All studies reported here were performed with dry ambient air* from a compressor unit. *Bronchodilator or other aerosols were not used.* Each test period lasted fifteen minutes; one-minute samples of expired gas were collected during the second, sixth, tenth, and fourteenth minutes and were analyzed for oxygen with a paramagnetic meter (Beckman) and for carbon dioxide with an infrared meter (Liston-Becker); expired volumes were measured with a Tissot spirometer and corrected to ambient pressure and saturated with water vapor (BTPS). During studies of the oxygen cost of breathing, gas collection periods were prolonged to three minutes, and expired gas was chemically analyzed.

The alveolar carbon dioxide tension (P_{ACO_2}) was recorded by continuous infrared analysis of expired gas by catheter sampling. The plateau values were checked at the end of each minute with the carbon dioxide tension obtained by a rebreathing maneuver (29) performed through a second arm of the five-way valve. This latter value, after subtraction of 6 mm. of mercury, always agreed with the end-tidal value within 1 to 2 mm. of mercury, except during intermittent positive pressure breathing without artificial resistance, when the rebreathing values were slightly but consistently higher; under these

[6] A standard, commercial, pressure-sensitive IPPB device with compressor unit was used for all of these studies; it produced a "Type III" curve (5, 7, 8).

circumstances the rebreathing value was chosen.

Effective *alveolar ventilation* ($\dot{V}_A$) was calculated from the equation

$$\frac{\dot{V}_{CO_2}\ (BTPS)}{\%\ \text{alveolar}\ CO_2} \times 100$$ and the *physiologic dead space* (V_D) from $$\frac{\dot{V}_E - \dot{V}_A}{\text{resp. rate}}$$ − apparatus dead space.

The functional residual capacity was measured as follows: After the rebreathing maneuver, the terminal three-way cock was turned so that successive expired tidal volumes were collected by the 9-liter recording spirometer. After five to seven expirations, the subject exhaled forcefully. From this last volume the expiratory reserve volume was calculated by subtracting from the forcefully exhaled volume the mean of the several preceding tidal volumes. The functional residual capacity was obtained by adding the expiratory reserve volume measured in this way to the residual volume previously determined by a modified nitrogen washout technique (30).

During the collection periods, *flow-rate* at the mouth was measured with a Silverman pneumotachograph screen connected to a Schaevitz differential pressure transducer. *Pressure at the mouth* (oral pressure) was measured with a similar, but less sensitive, transducer; and both signals were amplified and recorded by a conventional, multi-channel, direct-writing oscillograph. Flow and pressure calibrations were made at the beginning and at the end of each experiment.

The mechanical work of breathing through the *external system* was judged to be entirely against airflow (nonelastic) resistance because the extraluminal pressure was zero at no flow. The work was assumed to equal volume times mean pressure. The external mechanical work of expiration was calculated from the bag collection volume and the planimetrically determined mean pressure of an average expiratory pressure tracing. For calculation of the work of inspiration, the bag collection value was corrected to inspired volume in the usual manner. It was difficult to estimate the work of inspiration assisted by IPPB when pressures quickly became positive. This suggested that the subject was not performing work; yet, since the pressure curve for passive inflation of the chest was not known, the exact extent of actual work performed, if any, could not be determined. It was realized that such work as was recorded would give a low estimate.

Mean resistance to air flow was determined from mean pressure/mean air flow. During inspiration with intermittent positive pressure breathing, resistance was assumed to be present only if pressures became negative.

Occasionally, the response of obstructed subjects to different IPPB pressures was observed. For this the usual routine was altered so that the test period for each pressure lasted only eight minutes, and gas collections and other measurements were made during the last three minutes.

Intra-esophageal pressures were recorded with a long balloon (31) with subjects always in the sitting position to minimize artefacts (32). The pressure differences between balloon and mouth were recorded with transducers and technique described above.

Results

Respiratory gas exchange: Data of subjects breathing with and without artificial obstruction are shown in table 1 and are illustrated in figure 4. Subjects merely breathing through the circuit of figure 1 were called at *rest* in contrast to assisted breathing periods referred to as intermittent positive pressure breathing; and subjects who breathed without added resistance were called *normal*; those who responded to the standard external resistance with moderate respiratory insufficiency, *moderately obstructed*, and those with severe insufficiency, *severely obstructed*. The rationale for this subdivision of *obstructed* subjects will become apparent.

The following changes were observed when changing from *normal* to *obstructed* conditions: Minute and tidal volumes became slightly larger, the respiratory rate lower, and the functional residual capacities increased slightly (table 1). Because the physiologic dead space became larger, effective alveolar ventilation and $P_{A_{CO_2}}$ remained unaltered. Under both conditions all subjects were able to maintain a steady state

Neither *normal* nor *obstructed* subjects maintained a steady state when assisted by IPPB, as evidenced by the shift of respiratory exchange ratios. Assisted *normal* subjects demonstrated large and persistent changes of expiratory exchange ratios; unsteadiness was less marked under *obstructed* conditions and almost the same before and at the end of IPPB therapy (table 1). That IPPB was much less effective for the *obstructed* subjects could be shown by other data: Minute and tidal volumes rose only slightly (figure 4), the ratio of dead space to tidal volume (V_D/V_T) rose 18 per cent (compared with 10 per cent for *normal* subjects), and the ratio of effective alveolar to minute ventilation fell. The average drop of $P_{A_{CO_2}}$ after fifteen minutes' therapy was only 2 mm. of mercury (compared with a 12 mm. drop for *normal* subjects) and, unlike that in *normal* subjects, $P_{A_{CO_2}}$ continued to decrease only during the first few minutes of IPPB (figure 4).

TABLE 1

RESPIRATORY DATA

Subject	BSA*	Condition	$\dot{V}_E$†	V_D/V_T‡ × 100	f Respiratory Rate	$\dot{V}_A$§	FRC‖	P_{ACO_2}¶	$\dot{V}_{O_2}$**	Respiration Exchange Ratio
A. *Normal* (Unobstructed) Breathing										
Each subject: Mean of four one-minute periods										
	M²		*L./min.*	%		*L./min.*	*L.*	*mm./Hg*	*ml.*	
S. C.	1.62	Rest	8.4	30.3	13.0	3.8	1.76	38	268	0.70
		IPPB***	*20.5*	*28.1*	*17.6*	*12.0*	*1.75*	*24*	*286*	*1.45*
J. P.	1.76	Rest	7.0	29.9	12.5	3.0	1.64	40	229	0.73
		IPPB	*15.4*	*25.5*	*13.3*	*9.2*	*1.77*	*27*	*268*	*1.29*
E. G.	2.03	Rest	10.0	35.1	11.1	4.8	1.86	38	400	0.69
		IPPB	*19.3*	*40.0*	*15.0*	*9.4*	*1.87*	*29*	*374*	*1.04*
R. J.	2.18	Rest	10.6	28.1	12	5.7	3.43	41	454	0.74
		IPPB	*23.2*	*47.7*	*16.5*	*10.2*	*2.66*	*35*	*483*	*1.07*
J. Mcn.	2.00	Rest	10.2	33.5	11	5.0	2.31	41	338	0.84
		IPPB	*17.2*	*34.2*	*11.9*	*9.5*	*2.62*	*31*	*331*	*1.26*
Mean		Rest	9.2	31.4	11.9	4.5	2.20	40	338	0.74
Mean		IPPB	*19.1*	*35.2*	*14.9*	*10.1*	*2.13*	*29*	*348*	*1.22*
Each one-minute period: Mean of five subjects										
First minute		Rest	9.1	32.9	11.5	4.3	2.66	40	341	0.73
Second minute		Rest	9.1	31.3	12.1	4.3	2.17	40	321	0.76
Third minute		Rest	9.3	30.8	11.8	4.6	2.18	39	348	0.74
Fourth minute		Rest	9.2	31.1	12.0	4.4	2.13	39	330	0.75
First minute		IPPB	*21.2*	*34.9*	*14.6*	*11.1*	*2.22*	*32*	*359*	*1.50*
Second minute		IPPB	*19.2*	*36.2*	*15.3*	*9.3*	*2.12*	*29*	*346*	*1.25*
Third minute		IPPB	*17.7*	*36.2*	*14.7*	*8.4*	*2.11*	*28*	*350*	*1.06*
Fourth minute		IPPB	*18.3*	*34.7*	*15.0*	*8.9*	*2.09*	*27*	*339*	*1.07*
B. *Obstructed* Breathing										
Each subject: Mean of four one-minute periods										
S. C.		Obstructed	8.1	31.3	9.9	4.0	1.74	38	286	0.75
		IPPB	*9.7*	*37.5*	*10.7*	*4.5*	*1.67*	*36*	*270*	*0.84*
J. P.		Obstructed	7.5	32.9	11.5	3.3	1.54	40	230	0.80
		IPPB	*11.4*	*37.9*	*11.6*	*5.5*	*1.93*	*32*	*278*	*1.00*
E. G.		Obstructed	8.9	37.2	8.2	4.3	2.16	41	364	0.73
		IPPB	*11.5*	*38.0*	*8.1*	*6.0*	*2.50*	*35*	*364*	*0.86*
R. J.		Obstructed	11.2	40.3	12.1	5.0	3.69	43	455	0.68
		IPPB	*12.9*	*42.8*	*13.5*	*5.6*	*3.76*	*41*	*458*	*0.73*
J. Mcn.		Obstructed	11.2	31.2	11.8	5.8	2.22	39	370	0.86
		IPPB	*12.4*	*46.4*	*13.6*	*5.0*	*2.66*	*40*	*358*	*0.77*
Mean		Obstructed	9.4	34.6	10.7	4.5	2.27	40	342	0.76
Mean		IPPB	*11.6*	*40.6*	*11.5*	*5.3*	*2.50*	*37*	*346*	*0.84*
Each one-minute period: Mean of five subjects										
First minute		Obstructed	9.1	37.1	11.0	4.1	2.42	41	324	0.74
Second minute		Obstructed	9.4	35.0	10.8	4.5	2.31	41	341	0.78
Third minute		Obstructed	9.6	35.0	10.2	4.6	2.15	40	354	0.76
Fourth minute		Obstructed	9.5	32.6	10.9	4.7	2.25	39	349	0.77
First minute		IPPB	*11.7*	*39.6*	*11.1*	*5.5*	*2.45*	*37*	*350*	*0.89*
Second minute		IPPB	*11.3*	*38.0*	*11.5*	*5.5*	*2.55*	*36*	*345*	*0.86*
Third minute		IPPB	*11.7*	*45.8*	*11.2*	*5.0*	*2.42*	*36*	*349*	*0.79*
Fourth minute		IPPB	*11.2*	*43.3*	*11.5*	*5.3*	*2.58*	*37*	*339*	*0.83*

* BSA—body surface area

† $\dot{V}_E$—bag collection volume

‡ V_D/V_T—physiologic deadspace/tidal volume

§ $\dot{V}_A$—alveolar ventilation

‖ FRC—functional residual capacity

¶ P_{ACO_2}—alveolar carbon dioxide tension

** $\dot{V}_{O_2}$—Oxygen uptake per minute

*** All figures in italics refer to values obtained during breathing assisted by IPPB

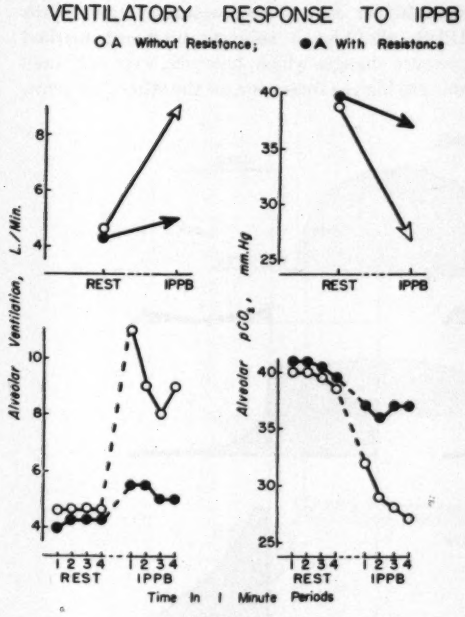


FIG. 4. Ventilatory response to IPPB of unobstructed and *obstructed* subjects. Mean changes are shown above, and progressive changes during the entire fifteen-minute test period are shown below. Mean data of 5 normal volunteers.

Individual responses of *obstructed* subjects to IPPB varied considerably (table 1). Subjects *J. P.* and *E. G.* raised their alveolar ventilation and lowered their $P_{A_{CO_2}}$ by clinically significant amounts; *R. J.* and *S. C.* obtained minimal benefit, while *J. M.* had a slight but definite progressive rise of $P_{A_{CO_2}}$ from 38 to 41 mm. of mercury.

The pressure-flow pattern at "rest": A typical "resting" pressure-flow breathing pattern is shown on the left in figure 5*A*, while the left side of figures 5*B* and *C* show patterns of *moderate* and *severely* obstructed subjects. Quantitative analyses for both groups are shown in table 1. The patterns of figure 5*B* of *J. P.* were almost identical to those inscribed by *S. C.* The patterns of 5*C* were extreme examples of tracings inscribed by *J. M.*; *R. J.* responded to obstruction qualitatively in similar fashion; the patterns of *E. G.* were intermediate between 5*B* and *C*.

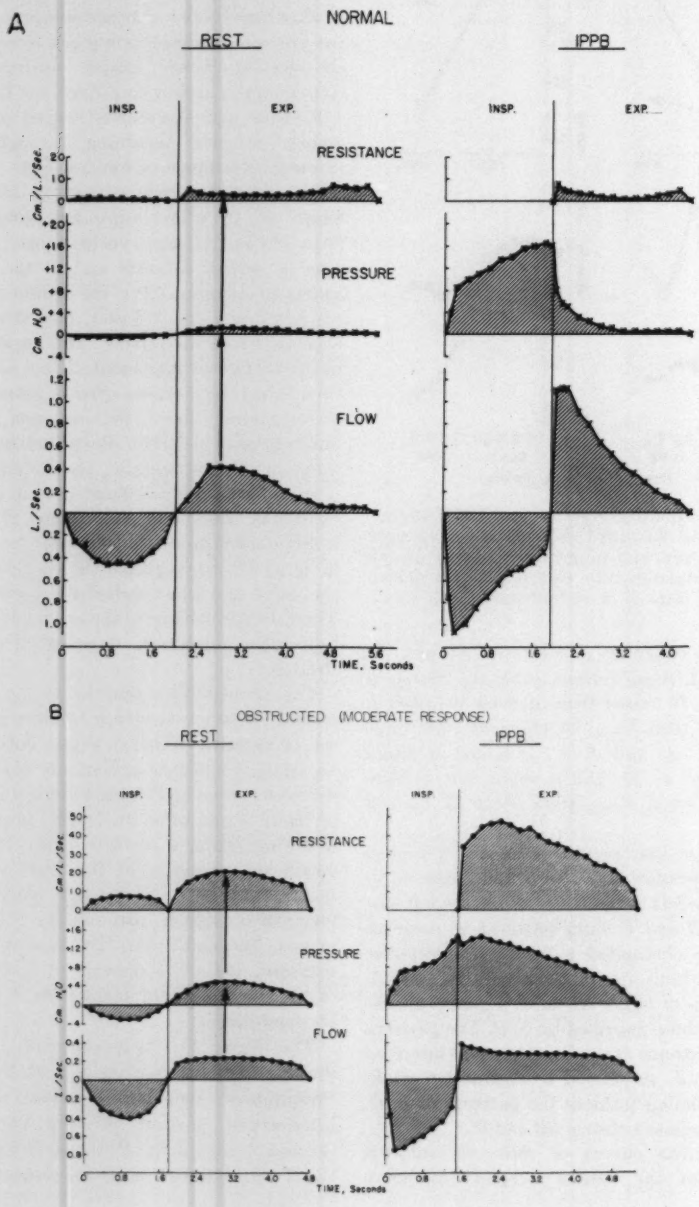
The flow-rate curves of *obstructed* subjects differed from the *normal* subjects in many important respects. Instead of a roughly sinusoidal pattern, flow was inscribed almost as a square wave. Expiration required a greater share of the total respiratory time; and peak inspiratory flows were greater and peak expiratory flows smaller than those for *normal* subjects. Obviously, the pressure required for a given rate of flow was considerably larger during obstruction and, consequently, airflow resistance was higher.

Pressure and flow curves varied considerably among subjects breathing through identical external resistance. Changes were most pronounced for those whose patterns are shown in figure 5*C* in whom expiratory pressures and flows did not change synchronously as was the case in *normal* subjects and in the *moderately obstructed* subjects. After the expiratory pressure reached 6 to 7 cm. of water, flow decreased and resistance rose excessively. This pressure, above which no further increment of flow occurred, has been called the *maximal effective pressure* and the corresponding flow, the *maximal flow rate*. Subjects with patterns illustrated by figure 5*B* were, in effect, breathing on the early, sloping portion of the pressure-flow curve of the variable expiratory resistance (*see* figure 2) and were called *moderately obstructed*. Subjects represented in figure 5*C*, who utilized the curving portion of the curve and who reached the vertical portion, where drastic collapse of the artificial "respiratory bronchiole" occurred, were called *severely obstructed*.

The pressure-flow patterns during intermittent positive pressure breathing assistance: The new set of patterns which emerged during pressure breathing tended to accentuate the differences between *normal* and *obstructed* subjects (right side of figure 5 and table 2). During obstruction the following changes occurred with IPPB: (*1*) a significant elevation of flow rate only during inspiration; (*2*) a lower oral pressure during inspiration, which rose during expiration to exceed, in each case, the maximal effective pressure; and (*3*) a consequent further increase of the fraction of the respiratory cycle required for expiration.

The degree to which *obstructed* subjects produced excessive narrowing of the artificial "respiratory bronchiole" before and during intermittent positive pressure breathing was estimated (figure 6). Without IPPB assistance the 3 subjects with *moderate obstruction* applied

pressures which rose only slightly above the maximal effective pressure and that for only a small fraction of the expiratory time. The other 2 produced greatly excessive pressures for more than 50 per cent of the expiratory time. With IPPB, the first 3 subjects produced marked pressure changes which, however, were only one-third as high as those seen for the other 2 subjects.



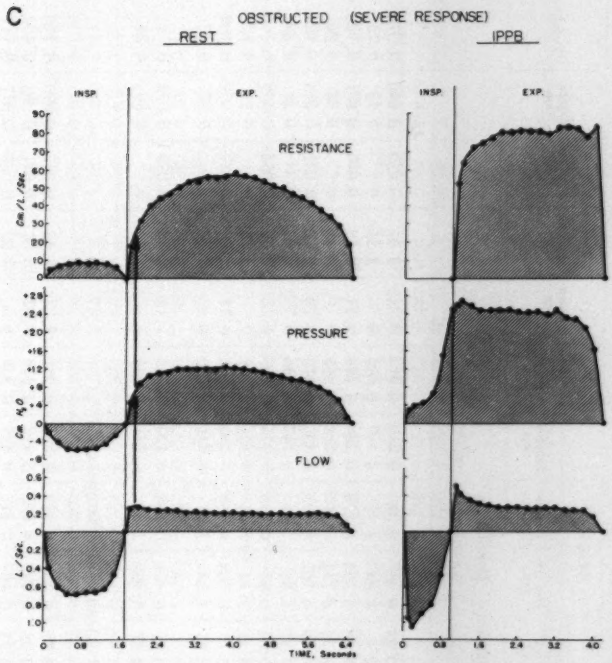


FIG. 5. Oral pressure, flow, and resistance patterns of unobstructed (A), moderately obstructed (B) and severely obstructed (C) subjects at rest and during IPPB. Arrows indicate pressure and resistance at maximal flow.

There was an inverse relation between the change in ventilation due to IPPB and the severity of airway closure. Subjects with flexible breathing patterns tolerated high end-inspiratory pressures and responded with a significant increase of ventilation. Conversely, those who showed "respiratory bronchiole" collapse without IPPB could not alter their rigid breathing pattern in response to IPPB and, consequently, their unassisted ventilatory performance was essentially their best.

Simultaneous machine and oral inspiratory pressures are plotted in figure 7. For unobstructed subjects, these pressures rose and fell in synchrony and were nearly of the same magnitude. In the *moderately obstructed* subjects, an initially high pressure gradient decreased progressively during inspiration; in the *severely obstructed*, oral pressure was *negative* during the first portion of inspiration, only to rise drastically at end-inspiration. These high gradients were the result of the pressure drop across the inspiratory resistance requiring early active inspiration.

The work of breathing: The methods of study just described were not suited for accurate measurement of *oxygen consumption* at "rest." During separate experiments with longer gas collection periods and chemical gas analyses, two patterns were observed as the result of resistance breathing: either oxygen uptake increased with maintenance of a normal $P_{A_{CO_2}}$ or oxygen uptake remained unchanged with concomitant underventilation and mild hypercapnia. These two types of response have been observed by others (33–35).

The *mechanical work* of breathing increased markedly as the result of external obstruction (table 1, figure 8). Unobstructed, unassisted subjects needed only 0.013 kg.-M. per liter of ventilation, while *obstructed* subjects required 0.10 kg.-M. or eight times as much external work to move the same volume. For each group, this work load was shared almost equally between inspiration and expiration (figure 8).

Intermittent positive pressure breathing was assumed to eliminate the inspiratory work for

TABLE 2

MECHANICAL DATA

Subject	Condition	Expiration of Time	Alveolar Pressure				Rate of Flow				Mean Resistance		Work		
			Maximal		Mean		Maximal		Mean						
			Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Total
A. *Normal* (Unobstructed) Breathing															
Each subject: Mean of four one-minute periods															
		%	*cm. H_2O*				*L/sec.*				*cm./L./sec.*		*kg.-M./L.*		
S. C.	Rest	66	−0.38	+1.0	−0.34	+0.53	0.41	0.33	0.412	0.214	0.812	2.47	0.029	0.045	0.074
	IPPB*	*51*	*+15.0*	*+16.9*	*+10.8*	*+2.6*	*0.88*	*1.10*	*0.700*	*0.668*	*0*	*5.35*	*0*	*0.75*	*0.75*
J. P.	Rest	61	−0.83	+2.10	−0.64	+1.16	0.325	0.375	0.300	0.189	2.14	6.12	0.045	0.081	0.126
	IPPB	*59*	*+12.9*	*+12.9*	*+9.61*	*+1.94*	*0.754*	*0.750*	*0.638*	*0.385*	*0*	*5.18*	*0*	*0.30*	*0.30*
E. G.	Rest	60	−0.53	+1.5	−0.30	+0.69	0.467	0.505	0.425	0.275	0.73	2.66	0.031	0.073	0.104
	IPPB	*58*	*+15.8*	*+14.1*	*+10.2*	*+2.4*	*1.04*	*1.06*	*0.767*	*0.553*	*0*	*4.25*	*0*	*0.46*	*0.46*
R. J.	Rest	62	−0.65	+1.00	−0.54	+0.83	0.65	0.398	0.475	0.285	1.16	2.91	0.055	0.090	0.145
	IPPB	*52*	*+15.0*	*+15.0*	*+9.22*	*+3.52*	*1.14*	*1.24*	*0.804*	*0.746*	*0*	*4.73*	*0*	*0.82*	*0.82*
J. Mcn.	Rest	65	−0.55	+1.30	−0.359	+0.67	0.504	0.481	0.486	0.260	0.74	2.56	0.037	0.069	0.106
	IPPB	*61*	*+18.1*	*+17.0*	*+14.0*	*+2.71*	*1.03*	*1.16*	*0.731*	*0.472*	*0*	*5.76*	*0*	*0.47*	*0.47*
Mean	Rest	63	−0.59	+1.4	−0.436	+0.77	0.471	0.418	0.420	0.245	1.12	3.34	0.039	0.072	0.111
Mean	IPPB	*56*	*+15.3*	*+15.2*	*+10.77*	*+2.63*	*0.969*	*1.06*	*0.728*	*0.565*	*0*	*5.11*	*0*	*0.56*	*0.56*
Each one-minute period: Mean of five subjects															
First minute	Rest	62	−0.61	+1.20	−0.47	+0.74	0.45	0.41	0.421	0.241	1.33	3.42	0.045	0.070	0.115
Second minute	Rest	63	−0.57	+1.34	−0.46	+0.78	0.46	0.40	0.413	0.240	1.17	3.36	0.041	0.063	0.104
Third minute	Rest	63	−0.62	+1.38	−0.43	+0.75	0.49	0.44	0.430	0.246	1.06	3.22	0.039	0.077	0.117
Fourth minute	Rest	62	−0.55	+1.54	−0.38	+0.83	0.49	0.43	0.413	0.245	1.02	3.53	0.035	0.076	0.110
First minute	IPPB	*55*	*+16.5*	*+15.9*	*+11.53*	*+2.95*	*0.976*	*1.12*	*0.788*	*0.601*	*0*	*5.16*	*0*	*0.63*	*0.63*
Second minute	IPPB	*57*	*+16.0*	*+15.4*	*+8.98*	*+3.01*	*0.989*	*1.06*	*0.753*	*0.572*	*0*	*5.32*	*0*	*0.60*	*0.60*
Third minute	IPPB	*56*	*+15.7*	*+14.9*	*+10.94*	*+2.65*	*0.944*	*1.01*	*0.670*	*0.536*	*0*	*4.86*	*0*	*0.50*	*0.50*
Fourth minute	IPPB	*56*	*+14.7*	*+14.5*	*+11.53*	*+2.75*	*0.960*	*1.03*	*0.670*	*0.549*	*0*	*5.10*	*0*	*0.52*	*0.52*

B. *Obstructed* Breathing

Each subject: Mean of four one-minute periods

S. C.	Obstructed	64	−5.0	+6.0	−3.5	+4.0	0.37	0.24	0.383	0.216	9.24	18.8	0.29	0.50	0.79
	IPPB	*71*	*+13.9*	*+13.9*	*+8.0*	*+5.7*	*0.64*	*0.35*	*0.569*	*0.224*	*0*	*25.5*	*0*	*0.56*	*0.56*
J. P.	Obstructed	64	−2.85	+5.0	−1.68	+3.32	0.400	0.24	0.345	0.194	4.90	17.2	0.13	0.25	0.38
	IPPB	*70*	*+14.0*	*+12.6*	*+8.92*	*+8.22*	*0.713*	*0.367*	*0.632*	*0.271*	*0*	*30.7*	*0*	*0.94*	*0.94*
E. G.	Obstructed	64	−5.5	+6.5	−3.6	+4.5	0.438	0.238	0.416	0.229	8.63	19.2	0.32	0.40	0.72
	IPPB	*75*	*+14.7*	*+13.6*	*+4.7*	*+8.6*	*0.896*	*0.363*	*0.764*	*0.256*	*0*	*33.7*	*0*	*0.98*	*0.98*
R. J.	Obstructed	71	−7.38	+9.8	−5.57	+8.05	0.660	0.262	0.651	0.264	8.56	30.4	0.63	0.91	1.54
	IPPB	*74*	*−2.3*	*+17.4*	*−1.73*	*+5.1*	*0.905*	*0.361*	*0.813*	*0.295*	*2.51*	*50.8*	*0.16*	*1.95*	*2.11*
J. Men	Obstructed	71	−6.4	+9.6	−4.96	+7.63	0.655	0.334	0.646	0.264	7.66	29.1	0.56	0.84	1.40
	IPPB	*76*	*+26.6*	*+26.6*	*+11.8*	*+22.0*	*1.00*	*0.442*	*0.861*	*0.274*	*0*	*80.6*	*0*	*2.74*	*2.74*
Mean	Obstructed	67	−5.4	+7.4	−3.9	+5.5	0.505	0.263	0.488	0.233	7.80	22.9	0.39	0.58	0.97
Mean	IPPB	*73*	*+13.4*	*+16.8*	*+6.3*	*+11.9*	*0.831*	*0.377*	*0.728*	*0.264*	*0.50*	*44.3*	*0.03*	*1.43*	*1.46*

Each one-minute period: Mean of five subjects

First minute	Obstructed	66	−5.1	+6.8	−3.43	+4.88	5.20	0.271	0.479	0.232	7.06	20.7	0.34	0.48	0.82
Second minute	Obstructed	65	−5.0	+7.1	−3.80	+5.63	4.92	0.267	0.470	0.238	8.02	23.0	0.38	0.56	0.95
Third minute	Obstructed	67	−6.0	+7.4	−4.15	+5.48	5.30	0.266	0.508	0.237	7.90	22.7	0.42	0.65	1.07
Fourth minute	Obstructed	69	−5.4	+8.3	−4.04	+6.16	5.03	0.256	0.514	0.230	7.77	25.7	0.40	0.63	1.03
First minute	IPPB	*75*	*+14.7*	*+18.7*	*+5.93*	*+14.2*	*0.853*	*0.394*	*0.775*	*0.264*	*0.66*	*5.27*	*0.044*	*1.17*	*1.78*
Second minute	IPPB	*73*	*+13.3*	*+17.2*	*+6.38*	*+12.8*	*0.825*	*0.366*	*0.728*	*0.263*	*0.93*	*43.2*	*0.052*	*1.37*	*1.42*
Third minute	IPPB	*73*	*+13.0*	*+16.4*	*+7.09*	*+11.6*	*0.812*	*0.383*	*0.727*	*0.270*	*0.42*	*42.6*	*0.03*	*1.41*	*1.44*
Fourth minute	IPPB	*72*	*+12.1*	*+14.9*	*+5.91*	*+10.3*	*0.837*	*0.363*	*0.681*	*0.258*	*0*	*38.4*	*0.00*	*1.21*	*1.21*

* All figures in italics refer to values obtained during breathing assisted by IPPB.

both groups (*see* "Methods"). Under these circumstances it cost unobstructed subjects only an additional 0.02 kg.-M./L. to increase ventilation 100 per cent; *obstructed* subjects were much less efficient: for the same additional work, ventilation increased only 37 per cent. This was as anticipated, for airway resistance rose by 21 cm. per L. per sec. in response to "respiratory bronchiole" collapse (figure 8).

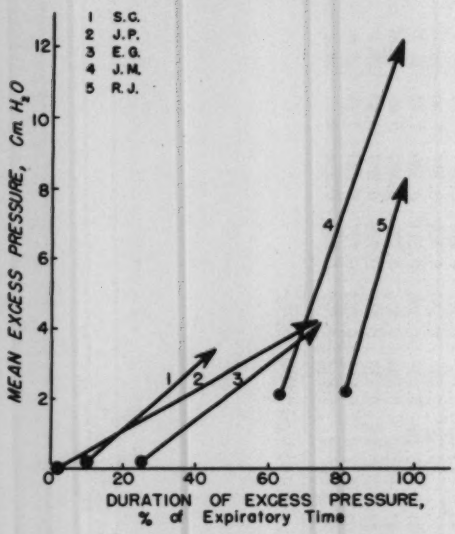


FIG. 6. Duration and magnitude of pressures, in excess of "maximal effective expiratory pressure" during expiration through variable resistance valve. Black dots indicate unassisted values and tips of arrows indicate IPPB values.

Mechanical work calculations from esophageal pressure measurements: Pressures recorded during routine studies reflected only the additional work against external resistance. For calculation of the total work of breathing, one subject was observed by intra-esophageal pressure measurements. Pressures recorded simultaneously from mouth and esophageal balloon are shown in figure 9.

Without external obstruction, the pressure tracings showed the expected variations due to changing elastic recoil. The compliance points are indicated at times of no flow. Total mechanical work, calculated from pressure-volume loops, was 0.32 kg.-M./min., and the resistive component represented only 30 per cent of this total. These figures agree with data of McIlroy and Christie (36) for normal subjects at rest. The actual total work of breathing of the unobstructed subjects was thus three times greater than that recorded for the external circuit of the routine studies quoted above.

During *obstructed* breathing, mouth and esophageal pressures became qualitatively similar (figure 9) because the differences due to the effect of changing elastic recoil were now relatively negligible. Under these conditions the total mechanical work of breathing was 1.36 kg.-M./min., and the resistive component represented 92 per cent of the total. From this it may be said that the work estimated for *obstructed* subjects during the routine studies reflected nearly all of the total work.

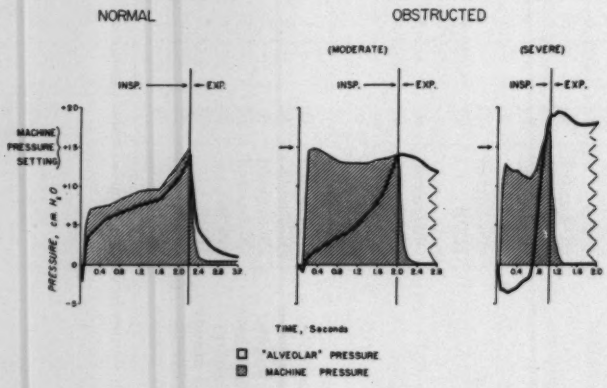


FIG. 7. Simultaneous machine and oral ("alveolar") pressures of unobstructed and moderately and severely obstructed subjects.

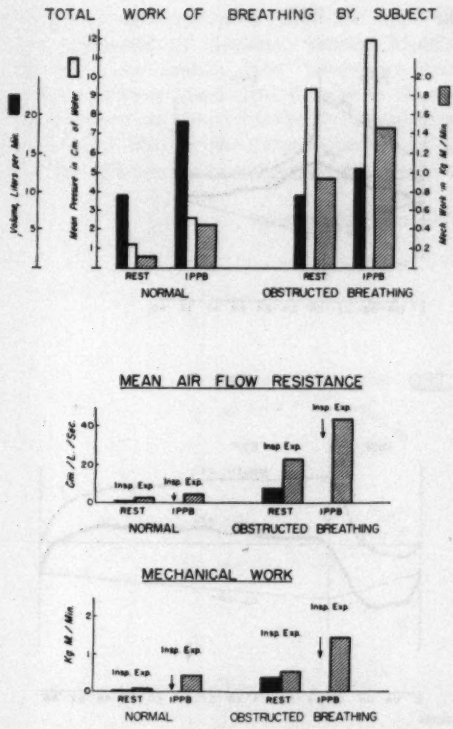


FIG. 8. External ventilation, mean oral pressure, and mechanical work of breathing of unobstructed (*normal*) and *obstructed* subjects breathing without assistance ("rest") and with "IPPB" (top). Mean airflow resistance (center) and mechanical work during inspiration and expiration, at "rest," and during "IPPB" (bottom).

In a clinical study (36) the total mechanical work of seven patients with severe emphysema at rest averaged 0.80 kg.-M./min. with a range of 0.38 to 1.54 kg.-M./min., which agrees quite closely with the present data. However, in the patients, only 62 per cent of the total work was against airflow resistance compared with the present estimate of 92 per cent. Obviously, the writers' external circuit merely raised flow-resistive work, while, in patients, the work against the elastic recoil also was abnormally great.

Effect of varying intermittent positive pressure breathing pressures: A rise of IPPB pressures to maximal levels at end-inspiration and a parallel rise of oral pressures prior to cessation of inspiratory flow were demonstrated in the present study. This high pressure, maintained early during *expiration*, caused "respiratory bronchiole" collapse whenever it exceeded the maximal effective pressure. It was thought that lower IPPB pressures than the usual 17.5 cm. of water might prevent this unfavorable sequence and permit greater flexibility of the breathing response. To test this hypothesis, one subject was studied at "rest" and during *obstructed* conditions with IPPB pressures of 7, 17.5, and 25 cm. of water (figure 10).

Maximal favorable change of $P_{A_{CO_2}}$ and alveolar ventilation occurred at the lowest pressure of plus 7 cm.! Here, oxygen consumption was smallest and the mechanical work of breathing was 15 per cent less than at rest. The fact that the functional residual capacity declined and the expiratory time was not increased further suggests that IPPB assumed a considerable portion of the work of breathing and allowed the subject to relax and adapt.

With larger pressures, intermittent positive pressure breathing became progressively more detrimental: at 25 cm. alveolar hypoventilation occurred even though mechanical work increased 250 per cent. The subject now actively fought the machine because he required peak inspiratory flow at a rate which the machine could not provide. Expiration now required 76 per cent of the total respiratory time, but even this was not sufficient to prevent excessive air trapping: the functional residual capacity rose 30 per cent above resting levels and now represented 73 per cent of the total lung capacity. These observations suggest why "assistance" at times may become physiologically and psychologically unbearable. They also suggest that increasing IPPB pressures may have the opposite of the desired result.

DISCUSSION

It had been hoped that intermittent positive pressure breathing would prove capable of augmenting ventilation in the severest phase of emphysema, but several reports suggest that treatment is often least effective at this juncture. In the present study of simulated pulmonary obstruction, such indeed was the case. Therefore, the first task was to consider how closely the expiratory valve simulated the obstructive breathing of asthma and emphysema.

A very large number of studies have been

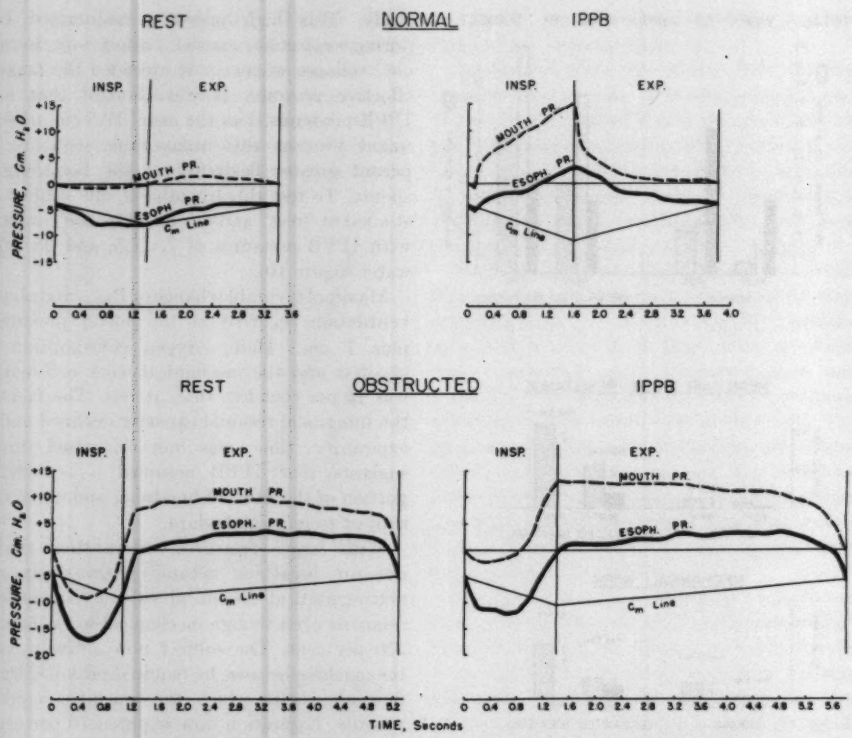


FIG. 9. Mouth and esophageal pressure breathing unassisted ("rest") and during IPPB, under unobstructed (*normal*) and *obstructed* conditions. The compliance points (no flow) are connected by (C_M) lines.

devoted to the effects of added external resistance on the cardiorespiratory system. A fixed resistance has been the natural choice when the effects of external breathing attachments such as gas masks were of primary concern. However, in the few studies oriented toward obstructive emphysema and/or respirators, the simulating resistance also has been of fixed intensity (37, 38) and thus not analogous to *obstructive* respiratory disease which involves conducting tubes of constantly varying length and diameter.

Recently, the complex relationship between airway resistance, lung tension, pressure drop, and air flow has been explored in more detail; and a number of electrical and mechanical analogues have been presented graphically to aid in the analysis of these relationships (26–28, 39). The simple model depicted in figure 1 represents an attempt at functional simulation of these events, using the normal human respiratory bellows and its complex regulatory mechanism as the driving pump.

The pressure-flow patterns reproduced here may be compared with patterns found by others in obstructive disease to evaluate the capacity of the variable resistance valve used in this laboratory to simulate certain of the mechanical consequences of bronchial asthma or emphysema.

Part *A* of table 3 shows the relative durations of inspiration and expiration observed by Mead and associates in severe emphysema (25, 31) and by Bouhuys in severe asthma and/or emphysema (40). There is a striking similarity between inspiratory/expiratory ratios of the present subjects and the patients. However, this response should be expected with any artificial resistance which is largely expiratory. The times required by the subjects in this study to reach peak

inspiratory and expiratory flows are equal to those measured by Bouhuys, whereas Mead's patients show slightly later inspiratory and earlier expiratory peaks (part *B*, table 3). Maximal pressures are attained earlier by the subjects in this study than by the patients (part *C*, table 3). This difference occurs because the pressure curves of the present writers reflect only resistance to airflow while, in the patients, the superimposed pressure required to overcome elastic recoil caused a delayed depression of the intra-esophageal pressure during inspiration and a belated elevation during expiration. Peak inspiratory and expiratory resistance, flow rates

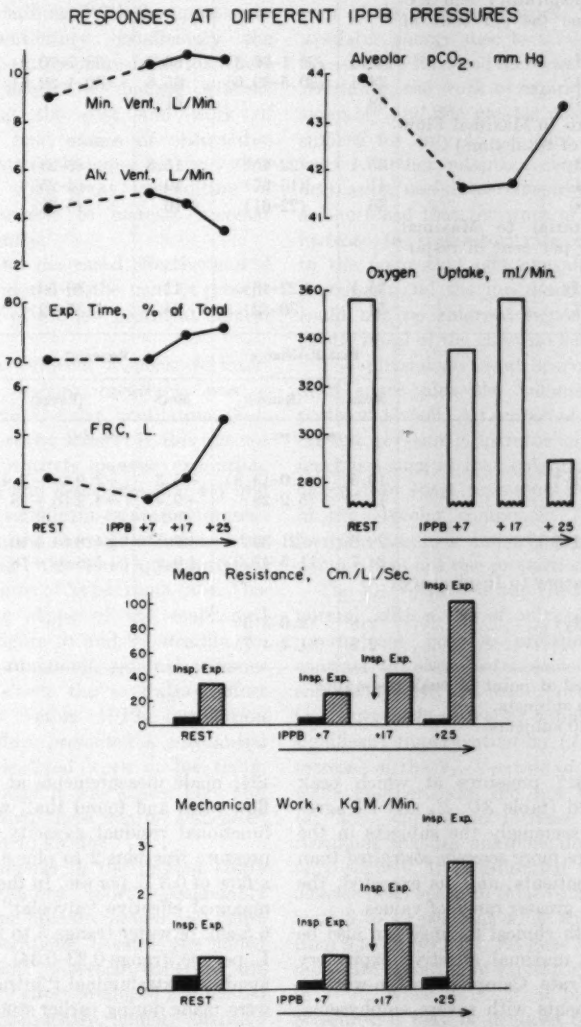


FIG. 10. External and alveolar ventilation, expiratory time as per cent of total respiratory time, functional residual capacity, alveolar CO_2 tension, oxygen uptake, airway resistance, and mechanical work during breathing with variable obstruction unassisted ("rest") and with IPPB set at +7, +17.5, and +25 cm. water pressure.

TABLE 3

RESPIRATORY CYCLE, PRESSURE, FLOW, AND FLOW-RESISTANCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE EMPHYSEMA AND IN "EXPERIMENTAL EMPHYSEMA"

	Inspiration		Expiration		Number of Subjects
	Mean	(Range)	Mean	(Range)	
	per cent		*per cent*		
A. Duration of Inspiratory and Expiratory Time (as per cent of total time)					
1. Present study	33.5	(29.1–36.3)	66.5	(63.7–70.9)	5
2. Mead (25, 31)	34.4	(30.5–39.6)	65.6	(60.4–69.5)	8
3. Bouhuys (40)	39		61		17
B. Time from Zero to Maximal Flow (as per cent of total time)					
1. Present study	35.1	(22–46)	15.8	(8–28)	5
2. Mead (25, 31)	41	(13–67)	10	(4–25)	8
3. Bouhuys (38)	36	(22–61)	16	(9–32)	17
C. Time from Initial to Maximal Pressure (as per cent of respiratory phase)					
1. Present study	35.1	(22–46)	41	(30–50)	5
2. Mead (25, 31)	54	(30–82)	64	(37–92)	8

	Peak Resistance		Pressure*		Flow*	
	Mean	(Range)	Mean	(Range)	Mean	(Range)
	cm./L./sec.		*cm. H_2O*		*L./sec.*	
D. Inspiration						
1. Present study†	10.5	(6.0–13.8)	−5.3	(−2.9 to −7.4)	0.5	(0.4–0.7)
2. Mead (25)‡	11.7	(5.2–26)	−9.4	(−4.2 to −18.2)	0.8	(0.6–1.0)
E. Expiration						
1. Present study†	29.0	(21–39)	+7.1	(+4.8 to +10.3)	0.2	(0.2–0.3)
2. Mead (25)‡	24.7	(11.5–47.0)	+9.9	(+5.8 to +18.4)	0.4	(0.2–0.8)
F. Ratio of Expiratory to Inspiratory Resistance						
1. Present study†	2.8	(2.0–3.5)				
2. Mead (25)‡	2.4	(1.3–4.7)				

* Values obtained at point of peak resistance.
† Averages for 5 subjects.
‡ Averages for 10 subjects.

and the "alveolar" pressures at which peak resistance occurred (table 3*D*, *E*, and *F*) agree well except that seemingly the subjects in the present study were more *severely obstructed* than the ambulatory patients; and, as expected, the patients showed a greater range of values.

Comparison with clinical findings can also be made concerning maximal effective expiratory pressure and flow rate. Campbell and co-workers (26), in four patients with severe emphysema, found during forced expiration a mean maximal effective pressure of plus 5.6 cm. of water (range 2.5–8.5) with a corresponding flow rate of 0.96 L. per sec. (range 0.58–1.26). Fry and associates (24) made measurements at relatively constant flow rates and found that, with breathing near functional residual capacity, maximal effective pressure was plus 2 to plus 4 cm. of water with a flow of 0.3 L. per sec. In the present study, the maximal effective "alveolar" pressure averaged 6.5 cm. of water (range 5 to 9), and the flow 0.3 L. per sec. (range 0.23–0.34). No direct measurements of extraluminal ("intrapleural") pressures were made during earlier studies; later measurements indicated an average maximal effective extraluminal pressure of 2–3 cm. of water. Although the conditions of the various studies were not strictly comparable, there is general

agreement between the present data from normal subjects, using the variable obstruction valve, and the data of others in obstructive emphysema.

In health the pattern of breathing is quite flexible, and large variations in airflow, external ventilation, respiratory rate, and inspiratory-expiratory time ratio can be experienced with only small changes in the oxygen cost or mechanical work of breathing. With the appearance of obstructive ventilatory insufficiency the breathing pattern becomes more rigid, and these variables can no longer be changed without significantly raising the cost and work of breathing. In the final stages of obstructive emphysema the pattern becomes so rigid that the patient, even with great expenditure of energy, may be unable to increase alveolar ventilation significantly.

Possible reasons for decreased effectiveness of IPPB may be considered in the light of present results and in view of the few pertinent clinical reports.

The unobstructed subjects' response to intermittent positive pressure breathing was a doubling of effective alveolar ventilation. Yet, contrary to the reports by some (15), this was not accomplished with entirely passive expiration. As shown by Fenn and associates (35, 41) and demonstrated here, significant expiratory muscular tone was maintained throughout most of the respiratory cycle, and this tone apparently increased with the degree of hypocapnia (35). This was shown by the shape of the esophageal pressure tracings (figure 9) and by steadily decreasing tidal and functional residual volumes during IPPB. In short, the expiratory effort began considerably before IPPB insufflation ceased, and this effort presented a substantial addition to the calculated work of breathing. This occurred although it was shown here and by others (41, 42) that there was no associated increase of resistance to air flow.

The *obstructed* subjects in the present study also initiated expiratory effort considerably before IPPB machine pressure ceased (*see* figure 9). Under these conditions, because the added "respiratory bronchiole" was easily collapsed, the premature expiratory effort produced augmented airway closure. Consequently, similar adaptive mechanisms produced different results in *obstructed* than in unobstructed subjects: the functional residual capacity enlarged, thereby increasing elastic and muscle fiber lengths; and the expiratory time was prolonged in an effort to allow more time for expiration.

These changes were thought to be compensatory and, by making certain assumptions (41, 43), the derived benefit can be calculated. Unassisted and without obstruction, the potential energy available at end-inspiration was about 0.55 kg.-M. which provided energy for about 80 per cent of the expiratory work. During IPPB, the available energy rose to 0.76 kg.-M. However. because IPPB caused increased expiratory airflow resistance, the work of expiration also rose considerably and the greater potential energy now sufficed for only 45 per cent of the expiratory work. Further adaptive changes might be of decreasing usefulness: Inspiration could not be so shortened that the work of inspiration would increase; the respiratory rate could not be slowed to the point that effective alveolar ventilation decreased; and the functional residual capacity could not be enlarged beyond a point where elastic recoil of the chest no longer existed (43).

The physiologic dead space is the anatomic dead space plus the volume of ineffectively perfused alveoli. A number of studies using the present pressure apparatus and other pressure machines suggest that enlargment of the physiologic dead space represents mainly an increase in the alveolar component (44–47). Such an increase assumes importance when the tidal volume does not rise proportionately.

The V_D/V_T ratio of the "resting" subjects was normal, with a rise of only 12 per cent during intermittent positive pressure breathing. In contrast, the *obstructed* subjects' ratio was slightly enlarged at rest, and rose 18 per cent with IPPB. One *moderately obstructed* subject, who achieved significant hyperventilation (*J. P.*), showed an increase of the V_D/V_T ratio of only 15 per cent, while another, who did not benefit by IPPB (*J. M.*), showed an increase of 50 per cent. Assuming that the anatomic dead space enlarges only slightly, it is estimated that the ratio of *alveolar* dead space to tidal volume for *J. P.* rose from 3 to 19 per cent while that for *J. M.* rose from 5 to 34 per cent. Because IPPB caused only moderate elevation of expiratory airway pressure in *J. P.*, while in *J. M.* it produced excessive pressures, it may be deduced that subjects with excess airway collapse develop positive intrathoracic pressure which in turn may lead to impaired distribution of pulmonary capillary blood flow.

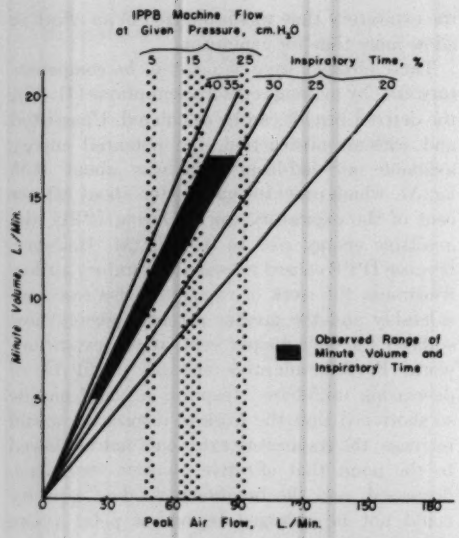


FIG. 11. Calculated peak inspiratory flow-rates (abscissa) required to produce a given minute ventilation (ordinate) at various percentages of respiratory cycle required for inspiration (diagonals) and assuming a sinusoidal flow pattern. The dotted columns represent observed IPPB machine flow rates at time of mid-inspiration at various indicated machine pressures, without obstruction to machine outflow. The width of the dotted columns indicates the slight increases in flow which occurred as the respiratory rate rose from 12 to 48 per minute. In this diagram, when machine flow-rate falls to the left of the subject's peak flow requirement inspiration requires active work in spite of assistance.

An invariable response to added expiratory resistance (with or without IPPB) was an increase of the fraction of the respiratory cycle required for expiration. The resulting reduction of inspiratory time required a rise of both mean and maximal inspiratory flow rates. The IPPB machine did not always provide a sufficient flow rate to allow entirely passive inspiration (figure 7). This prompted the writers to examine its pressure-flow characteristics. It may be seen in figure 11 that, when the outflow tube of the machine was open to the room, barely adequate peak flow rates were obtained for the observed resting ventilatory requirements. When the machine delivered air through the fixed inspiratory obstruction (or conceivably, through a tracheostomy tube or tracheobronchial tree encumbered by secretions, spasm, and edema) there was a reversal of the low pressure-high flow characteristic and peak flow was sharply decreased: at the same machine pressure setting, flow rate dropped to 60 per cent of the unobstructed value. The machine then was no longer capable of delivering peak flow rates sufficient for entirely passive inspiration.

Without a doubt, intermittent positive pressure breathing is capable of inducing sustained hyperventilation in normal subjects and of raising alveolar ventilation in patients with respiratory muscular paralysis or those with diffuse respiratory obstruction of moderate severity. The present studies suggest that, with expiratory obstruction simulating that encountered by patients with severest obstructive ventilatory insufficiency, conventional IPPB machines may be incapable of augmenting alveolar ventilation. This is largely because the very high end-inspiratory alveolar pressures, compounded by machine and premature expiratory effort during insufflation, cause a transpulmonary pressure which is greatly in excess of the maximal effective pressure (26). As a result there is drastic airway closure and "trapping." Under these circumstances, hypercapnia is not relieved even if ventilation is slightly increased: in part, because the now greater work of expiration more than compensates for any slight increase in alveolar ventilation and, in part, because increased physiologic dead space may negate any increment of external ventilation achieved. Finally, the greater the IPPB pressure under these circumstances, the more detrimental the results.

The laboratory finding of increased expiratory resistance during IPPB may be reflected clinically by: a decrease of respiratory rate, a rise of functional residual capacity (37, 48), or by persisting hypercapnia despite increased ventilation. Clinically, all three responses have been demonstrated. In the study by Cullen and associates (18) three of the five patients with emphysema who had persistent hypercapnia with IPPB showed a decrease of respiratory rate. In the present writers' experience, 3 of 4 patients who failed to benefit from IPPB reacted with a fall in rate while 3 of 4 who improved did not. Other reports document increased air trapping during IPPB (20, 49, 50) which may become so severe that effective ventilation is decreased and "therapy" becomes intolerable. Finally, Motley and co-workers (11) showed that the V_D/V_T ratio rose 26 per cent in twenty-eight patients who

had an insignificant lowering of P_{ACO_2} with IPPB, while this ratio rose only 13 per cent in twenty-one patients in whom P_{ACO_2} dropped an average of 9 mm. of mercury, despite the fact that the increment of minute ventilation was similar for both groups.

Occasional failure of IPPB in severest obstructive ventilatory insufficiency is reported by its most enthusiastic supporters. For example, Sieker and Hickam (51), in their excellent review of the problem of carbon dioxide intoxication, report a mortality of 53 per cent in thirteen patients treated for carbon dioxide narcosis during a four-year period when artificial ventilation was not used. However, their mortality was 50 per cent among twelve similar patients intensively treated with IPPB during the next two-year period. From theoretic considerations and results with lung models with fixed resistances, their Seeler respirator was designed to deliver very low peak flow rates (in the order of 15 to 30 L. per min.) and with "as high mask pressure as is compatible with safety" (about 30 cm. of water) (38). The present experiments would suggest why, in their experience, this respirator would "not permit its comfortable use in many patients who are conscious" (51). Extensive use of the much more sophisticated Engström respirator produced excellent results in a large variety of acute respiratory failures; however, the over-all mortality in emphysema with carbon dioxide narcosis was again 47 per cent (52).

Intermittent positive pressure breathing is so poorly tolerated by some conscious or semicomatose patients that some clinicians have advocated induction of respiratory muscular paralysis by heavy sedation (53), general anesthesia, or curare (54), followed by resuscitation with fully automatic breathing pumps. Short of this, the present study suggests design of a patient-cycled respirator which can deliver very high peak flow rates (in excess of 80 L. per min.), which has a decreasing—rather than an increasing—pressure through the inspiratory cycle, thus leaving the alveoli with a low end-inspiratory pressure; and one which is sensitive enough to permit complete freedom of choice of respiratory rate. A negative expiratory phase, if used at all, must not be greater than that required to overcome the fixed resistance of external breathing devices. If greater, it would serve to increase the alveolar-mouth pressure drop and thus would tend to augment airway closure.

Summary

Clinical experience suggests that mechanical assistance with intermittent positive pressure breathing (IPPB) fails to improve alveolar ventilation in about one-half of all patients with severest emphysema in acute respiratory failure. The inability of the writers to study all parameters of ventilation and gas exchange before and during IPPB in these very ill patients suggested the design of a variable resistance valve which would simulate their type of expiratory obstruction.

The pressure-flow relationship of this valve was fairly linear up to a flow of 10 L. per min. Thereafter flow increased little while pressure rose from 4 to 35 cm. of water; still higher pressures decreased the rate of flow. Normal subjects breathing through this valve showed changes of pneumotachogram, inspiratory-expiratory time ratio, functional residual capacity, dead space, expiratory flow resistance, maximal effective expiratory pressure, and the mechanical work of breathing all very much like those of patients with severe chronic obstructive disease.

Five normal subjects were studied repeatedly with and without obstruction and with and without IPPB assistance. Without obstruction, IPPB easily doubled alveolar ventilation. Oral and machine pressures moved in synchrony, the physiologic dead space increased slightly, and hypocapnia developed rapidly.

During obstructed breathing without IPPB, the mechanical work of breathing increased eightfold; work required to overcome flow resistance increased from 30 to 92 per cent of total work; respiratory rate decreased; and external ventilation, physiologic dead space, and functional residual capacity all increased slightly. Alveolar ventilation and carbon dioxide tension remained unaltered, and a steady state was maintained.

During obstructed breathing assisted by IPPB, flow rate increased only during inspiration, and expiration became greatly prolonged. Most striking was markedly increased expiratory flow resistance, chiefly due to very high end-inspiratory alveolar pressure, compounded by machine and premature expiratory effort during insufflation; this induced a transpulmonary pressure drop greatly in excess of maximal effective pressure, causing airway closure, "trapping," and greatly increased work of expiration. Although

potential energy built up during inspiration increased, it now sufficed for only 45 instead of 80 per cent of the expiratory work. Although minute ventilation increased somewhat, pulmonary aeration was not improved. This was, in part, because increased gas exchange was more than compensated for by the greater work required for expiration and, in part, because of increased physiologic dead space. The latter suggested impaired distribution of blood flow.

With low IPPB pressures (7 cm. of water) the work of breathing was 15 per cent less than without assistance, a steady state was maintained, and there was no rise of functional residual capacity. At the highest pressures (25 cm. of water) there was marked alveolar hypoventilation although the mechanical work of breathing increased 250 per cent over unassisted levels; peak machine flow was insufficient for passive inspiration; and functional residual capacity and physiologic dead space increased greatly. This suggested why "assistance" at times may be physiologically and psychologically unbearable and why increasing IPPB pressures may have the opposite of the desired result.

These data suggest design of a patient-cycled respirator capable of delivering very high flow rate at pressures which are decreasing rather than increasing during the inspiratory cycle and which is sensitive enough for free choice of respiratory rate. A negative expiratory phase would increase the transpulmonary pressure drop and thus aggravate airway closure.

Sumario

Los Efectos de la Respiración a Presión Positiva Intermitente en la Oclusión Pulmonar Simulada

Sugiere la observación clínica que la ayuda mecánica prestada con la respiración a presión positiva intermitente (RPPI) no mejora la ventilación pulmonar aproximadamente en la mitad de todos los enfermos que padecen del enfisema más grave en la insuficiencia respiratoria aguda. La incapacidad de los AA. para estudiar todos los parámetros de la ventilación y del intercambio de gases antes de la RPPI y durante ésta en estos enfermos gravísimos sugirió el diseño de una válvula de resistencia variable que simulara la clase de oclusión espiratoria que tenían.

La relación de la presión-corriente en esta válvula fué bastante lineal hasta llegar a una corriente de 10 L. por min. A partir de ahí, la corriente aumentó poco mientras que la presión se elevó de 4 a 35 cm. de agua; presiones todavía más altas mermaron la velocidad de la corriente. Los sujetos normales que respiraron a través de esta válvula revelaron alteraciones del neumotacograma, de la proporción del tiempo aspiratorio-espiratorio, la capacidad residual funcional, del espacio desvitalizado, la resistencia a la corriente espiratoria, la presión espiratoria eficaz máxima y la labor mecánica de la respiración en forma muy semejante a la mostrada por los sujetos que padecían de enfermedad oclusiva crónica grave.

A 5 sujetos normales se les estudió repetidamente con y sin oclusión y con y sin RPPI. Sin oclusión, la RPPI redobló fácilmente la ventilación alveolar. Las presiones oral y con aparato (maquinal) se movieron sincrónicamente, el espacio desvitalizado fisiológico aumentó ligeramente y apareció rápidamente hipocapnia.

Durante la oclusión respiratoria sin RPPI, la labor mecánica de la respiración se octuplicó; el trabajo necesario para vencer la resistencia a la corriente aumentó de 30 a 92 por ciento del trabajo total; la velocidad respiratoria disminuyó y aumentaron ligeramente la ventilación externa, el espacio desvitalizado fisiológico y la capacidad residual funcional. Permanecieron inalteradas la ventilación alveolar y la tensión del bióxido de carbono y se mantuvo un estado constante.

Durante la oclusión respiratoria ayudada por la RPPI, no aumentó la velocidad de la corriente más que durante la aspiración y la espiración se prolongó considerablemente. Lo más notable fué el decidido aumento de la resistencia a la corriente espiratoria, debido principalmente a la elevadísima presión alveolar al final de la aspiración, reforzado por el esfuerzo espiratorio maquinal y prematuro durante la insuflación; esto provocó ina baja de la presión transpulmonar que excedió considerablemente la presión eficaz máxima, ocasionando cierre de las vías aéreas, "atrape," y mucho aumento de la labor espiratoria. Aunque aumentó la energía potencial acumulada durante la aspiración, no bastaba entonces más que para 45 en vez de 80 por ciento de la labor espiratoria. Si bien aumentó algo la ventilación por minuto, no mejoró la aireación pulmonar. Esto sucedió, en parte porque el aumento del intercambio gaseoso quedó más que compensado por la mayor labor requerida para la espiración y, en parte, debido al aumento del espacio desvitalizado fisiológico. Lo último indicaba menoscabo de la distribución del torrente sanguíneo.

Con presiones bajas de la RPPI (7 cm. de agua), la labor respiratoria fué 15 por ciento menor que sin ayuda, se mantuvo un estado constante y no hubo ascenso de la capacidad residual funcional. A las presiones más altas (25 cm. de agua), hubo acentuada hipoventilación alveolar, aunque la labor mecánica de la respiración aumentó en

250 por ciento, comparado con las cifras obtenidas sin ayuda; la corriente maquinal máxima resultó insuficiente para la aspiración pasiva y aumentaron considerablemente la capacidad residual funcional y el espacio desvitalizado fisiológico. Esto sugería por qué la "ayuda" puede a veces resultar fisiológica y psicológicamente intolerable y por qué el aumento de las presiones de la RPPI puede producir lo contrario del efecto deseado.

Sugieren estos datos el diseño de un respirador de ciclos para enfermos, capaz de transmitir una corriente de mucha velocidad a presiones que bajen más bien que suban durante el ciclo aspiratorio y que sea suficientemente delicado para permitir la selección libre de la velocidad respiratoria. Una fase de espiración negativa acrecentaría la baja de la presión transpulmonar, agravando así la clausura de las vías aéreas.

Resume

Les effets de la respiration sous pression intermittente positive dans des cas simulés d'obstruction pulmonaire

L'expérience clinique fait penser que l'aide mécanique d'une respiration sous pression positive intermittente (IPPB) n'arriva pas à améliorer la ventilation alvéolaire chez à peu près la moitié de tous les malades avec emphysème et défaillance respiratoire aiguë. L'impossibilité des auteurs d'étudier tous les paramètres de la ventilation et des échanges gazeux avant et pendant l'IPPB, chez les sujets très malades, a fait penser à créer une valve à résistance variable, qui simulerait leur type d'obstruction expiratoire.

On trouva une relation passablement linéaire entre le débit et la pression, jusqu'à un débit de 10 L/min. Après cette valeur, le débit augmenta peu tandis que la pression monta de 4 à 35 cm d'eau; des pressions supérieures décrurent le taux de débit. Des sujets normaux, respirant à travers cette valve, montrèrent des changements du pneumotachogramme, du rapport temps d'expiration-temps d'inspiration, de la capacité résiduelle fonctionnelle, de l'espace mort, de la résistance au débit expiratoire, et de la pression effective maxima d'expiration; le travail mécanique de la respiration se montra, en gros, très similaire à celui des malades ayant une grave obstruction chronique.

Cinq sujets normaux furent étudiés à plusieurs reprises, avec et sans obstruction, avec et sans l'aide de l'IPPB. Sans obstruction, l'IPPB doubla facilement la ventilation alvéolaire. Les pressions de la bouche et de la machine se déplacèrent synchroniquement, l'espace mort s'accrût légèrement et de l'hypocapnée se developpa rapidement.

Pendant la respiration avec obstruction sans IPPB, le travail mécanique de la respiration augmenta de huit fois; le travail requis pour vaincre le résistance du débit augmenta de 30 à 92% du travail total; le rythme respiratoire décrut; la ventilation externe, l'espace mort physiologique et la capacité fonctionnelle résiduelle, toutes ces données augmentèrent légèrement. La ventilation alvéolaire et la tension du dioxide de carbone restèrent inchangées et un état stable fut maintenu.

Pendant la respiration avec obstruction et avec l'aide d'IPPB, le taux du débit augmenta seulement pendant l'inspiration, et l'expiration s'allongea beaucoup. Le plus frappant fut l'augmentation marquée de la résistance au flot expiratoire, due principalement à la très haute pression alvéolaire en fin d'expiration à la fois due à la machine et à l'effort prématuré d'expiration pendant l'insufflation; ceci entraina une chute de la pression transpulmonaire en plus de la pression effective maxima, causant la fermeture des voies aériennes, "gardant l'air prisonnier", et accrut beaucoup le travail d'expiration. Bien que le potentiel d'énergie établi pendant l'inspiration augmenta, il ne procura alors que 45% du travail expiratoire au lieu de 80%. Ceci fut dû en partie au fait que l'augmentation des échanges gazeux fut plus que compensé par le travail plus grand requis pour l'expiration, et, en partie, à cause de l'augmentation de l'espace mort physiologique. Ce dernier fait penser qu'il y a une atteinte de la distribution du débit sanguin.

Avec des pressions basses d'IPPB (7 cm d'eau), le travail de respiration fut de 15% moins grand que sans cette aide, un statu quo fut maintenu et il n'y eut pas d'augmentation de la capacité fonctionnelle résiduelle. A de très hautes pressions, (25 cm d'eau), il y eut une hypoventilation alvéolaire nette, bien que le travail mécanique de respiration augmenta de 250% par rapport à celui des cas non aidés. Le maximum de débit de la machine fut insuffisant pour une respiration passive; la capacité fonctionnelle résiduelle de l'espace mort physiologique augmentèrent beaucoup. Ceci suggère pourquoi "l'aide" peut parfois être physiologiquement et psychologiquement insupportable et pourquoi des pressions de plus en plus hautes d'IPPB peuvent aller à l'encontre du résultat désiré.

Ces données font penser à un système d'appareil faisant respirer le malade dans un circuit capable de fournir un taux de débit très élevé, à des pressions que sont plutôt décroissantes pendant le cycle inspiratoire, et qui est assez sensible pour choisir de lui-même le rythme respiratoire. Une phase expiratoire négative augmenterait la chute de pression transpulmonaire et aggraverait ainsi la fermeture des voies aériennes.

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ISOLATION AND STUDY OF THE ELASTIC TISSUE NETWORK OF THE LUNG IN THREE DIMENSIONS[1, 2, 3]

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INTRODUCTION

The elastic properties of the lung have been recognized as important in respiration for many years. The relation of pulmonary structure to pulmonary function, and particularly to the elastic recoil of the lung, is not, however, clearly understood. Since Von Neergaard's work (1) it has been thought that pulmonary retractility is due partly to surface forces and partly to the elasticity of tissue components (2). Of the tissue factors, elastic connective tissue is probably important in determining pulmonary elastic recoil, although no rigorous proof of its functional significance is available. The notion of its elastic role in the retractility of the lung rests upon the following evidence: Elastic tissue is known to have long-range reversible extensibility (3); it is present in significant quantities in all parts of the lung which are thought to expand and in all mammalian species which have been examined (4); by analogy, it is a major component of other reversibly extensible organs, such as large arteries and skin (5).

If, then, elastic tissue might have such importance, it may be wondered how it is distributed in the lung, what variations occur between one individual and another, and how it is altered in diseases involving decrease in elasticity. Orsos (6), Sudsuki (7), and other anatomists have stained thin sections of normal and emphysematous human lungs with specific elastic tissue stains (Weigert's, orcein, et cetera) and have described the distribution of elastic tissue in the tracheobronchial tree, terminal air spaces, pleura, and pulmonary vasculature (figure 1).

The interpretation of these conventional sections suffers in that the fibers cannot be traced for any significant distance in three dimensions, and their relation to air spaces and to blood vessels is not fully disclosed. Also, no reliable analysis can be made of the chemical and physical properties of the elastic tissue once the tissues have been fixed and stained. To avoid the first of these difficulties, Miller (8) made three-dimensional reconstructions from serial sections. These showed the rich elastic network in the alveolar walls and the distribution of the supporting elastic framework in the branches of the tracheobronchial tree in normal human lungs. These reconstructions are laborious to assemble, and only a few have been made. As a consequence, there is inadequate understanding of the three-dimensional structure of pulmonary elastic tissue in emphysema and other chronic lung diseases in which disturbances of elasticity would seem to be important.

The present writers have isolated the pulmonary elastica by the use of concentrated organic acids in a manner similar to that previously used (9, 10) for isolation of the elastica of blood vessels. The method allowed the pulmonary elastic network to be examined in three dimensions. A large number of specimens could be handled easily, and similarly treated material could be subjected to analysis by other than microscopic methods.

METHODS

In order to isolate the pulmonary elastica in the form in which it exists in the body, the following steps were required: (*1*) separation of elastic tissue from the other tissue components; (*2*) mounting and preservation of this delicate network in three dimensions without substantial distortion.

(*1*) *Separation:* Sodium hydroxide (11), boiling water (3), and proteolytic enzymes (12) have been used in the isolation of elastica. Concentrated formic acid was selected as a differential agent because it leaves the elastic fiber intact while

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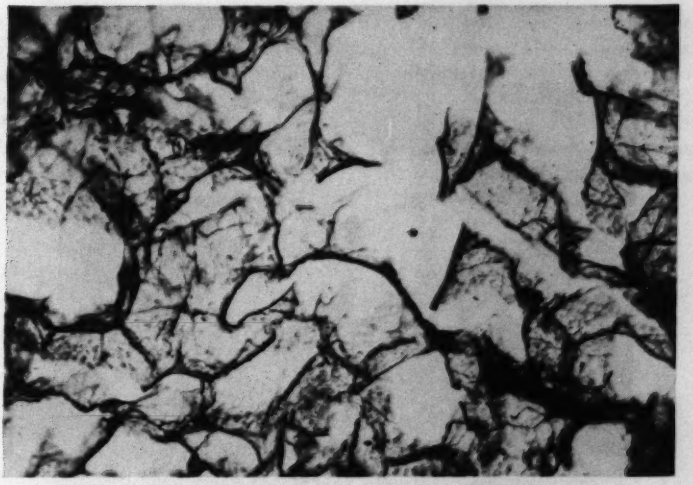

FIG. 1. A thick (40 microns) section of normal human lung, fixed in 10 per cent formalin without digestion by formic acid. The elastic fibers are stained to appear dark. This section, prepared by conventional histologic technique, serves as a control for comparison with subsequent illustrations. (Weigert's resorcin-fuchsin, 140 ×)

dissolving all other pulmonary structures except the matrix of cartilage and pigment deposits. All parts of the lung can be brought simultaneously into contact with the reagent, thus making it an ideal organ for corrosion preparations of this kind.

Blocks of tissue, 1.5 cm. in all dimensions, were taken from the parenchyma of human lungs at autopsy. Forty separate specimens were examined, the age of the subjects ranging from eighteen to eighty-two years. The majority were in the older age groups. All died from nonpulmonary causes. No correlation of structure with age, sex, or race was attempted. Large bronchi were avoided because of cartilage. (In some instances the lungs had been fixed in 10 per cent formalin for twenty-four hours. This made the networks more rigid, and some structures more resistant to the reagent.) The blocks were then placed in 90 ml. of 88 per cent formic acid at 45°C. for seventy-two hours, after which the residue was washed in running tap water for one hour. Porous tea-steepers of 200-ml. capacity were found ideal for holding the tissue during this stage. Following staining for twenty minutes in aqueous basic fuchsin (0.5 per cent), the mass was seen to consist of intertwining fibers which retained the basic architecture of the lung. Immersion of the fibers in alcohol and other drying substances caused them to shrink severely; hence an aqueous technique was used throughout.

(*2*) *Mounting and preservation:* Mounting presented the problem of fixing and preserving the tissue in three dimensions without distortion of the delicate network floating in water.

The blocks were immersed in two changes of warm 10 per cent gelatin in water for thirty minutes each. At the end of the second thirty minutes the gelatin was chilled and allowed to solidify in a refrigerator overnight. The firm gelatinous mass was then released from its paper container and hardened in 10 per cent formalin for two days, following which thick sections were cut free-hand with thin razor blades and preserved in 10 per cent formalin. By this time there was no appreciable diffusion of the basic fuchsin into the gelatin.

These gelatin mounts have been kept without losing stain or other change and can easily be examined under the binocular dissecting microscope, even after six months. It must be assumed in the use of this method that the fibers spread out in liquid in a "rest" position and that this position approximates that taken in the living lung. This assumption seems reasonable because of the resemblance of the distribution of these isolated fibers to those reconstructed from serial sections, in which the other pulmonary elements are available for support.

As an alternative, the blocks of elastic tissue were frozen in ice following staining and the ice was then sublimated by the freeze-dry technique, leaving the dry network behind to be sectioned freehand and embedded in ethyl methacrylate. This method yielded permanent preparations, but distortion was considerable, so that gelatin embedding was the preferred method.

Some specimens were examined under the electron microscope after corrosion by formic acid. In these instances the neutralized elastic tissue network was fixed in osmic acid, dehydrated in an

FIG. 2. Elastic fibers from normal human lung, as isolated with concentrated formic acid and fixed in osmic acid. (Electron photomicrograph, 3000 ×)

ascending alcohol series, and embedded in a mixture of butyl and ethyl methacrylate. Very thin sections were then taken for electron microscopic examination.

RESULTS

Is this isolated material actually elastic tissue? Elastica has been isolated from the aorta by similar means (9); this material from the lung is highly extensible when teased; it retains the distribution usually associated with pulmonary elastica (4); it accepts the Weigert elastic stain readily; electron photomicrographs of the material (figure 2) show a homogeneous fiber structure consistent (13, 14) in appearance with elastic tissue and an absence of other recognizable tissue elements, except cartilage matrix, rarely included in the blocks. Pigment deposits also were not entirely dissolved and often persisted, particularly around the pulmonary arteries and veins, presumably in relation to the distribution of lymphatics.

Is the form of the elastic tissue of the lung preserved in these thick sections? Judged from the appearance under the conventional two-dimensional microscope, the answer would be in

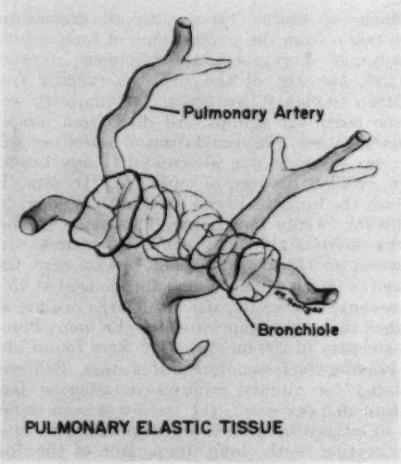

FIG. 3. A drawing of a small bronchiole and the accompanying branch of the pulmonary artery. These are shown coming from below up toward the reader. Note the "hoops" and the proximity of bronchiole and artery. Formic acid corrosion preparation from a block of normal human lung. (60 ×)

the negative. If, however, key structures are selected, i.e., blood vessel, bronchiole, alveolar duct, alveolus, and pleura, and examined under a dissecting microscope, a much clearer picture of the elastic network presents itself. One area after another has been selected and, in drawings supplemented by photographs, the anatomic relationships have been shown as they appear in three dimensions. The elastica of the branches of the pulmonary artery is preserved down to about a diameter of 50 microns (figure 3). The small branches are regularly accompanied by bronchioles, and this complex of artery and bronchiole is the major landmark in identifying the lobular

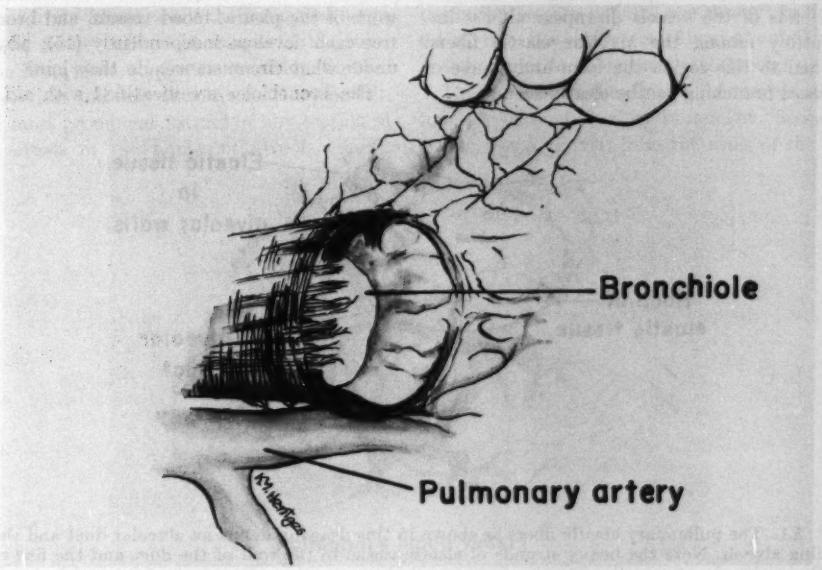

FIG. 4A. A drawing of a small bronchiole. Both the oblique and the longitudinal elastic networks in the bronchiolar wall are shown. No alveolar mouths appear along the wall of this bronchiole; it is a terminal bronchiole. Note the accompanying branch of the pulmonary artery. Formic acid corrosion preparation of a block of normal human lung. (45 ×)

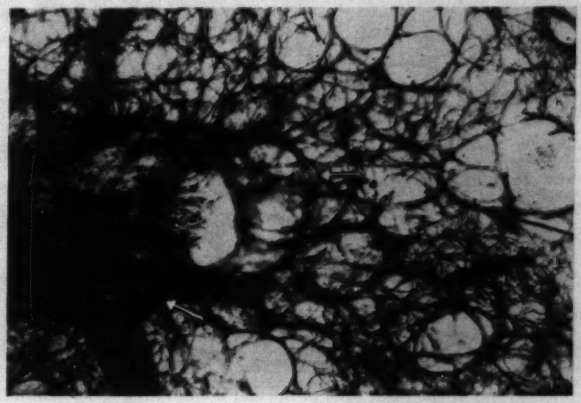

FIG. 4B. A photomicrograph of the same area as drawn in figure 4A. Formic acid corrosion preparation designed to show only the pulmonary elastic tissue network. The arrows refer to the bronchiole and the branch of the pulmonary artery, as identified in figure 4A. (65 ×)

structure of the elastic network. The pulmonary veins, on the other hand, are not accompanied by large air channels and are located at a relatively great distance from the branches of the pulmonary artery. An elastic residue corresponding to the bronchial arteries is not identified. The elastica of the blood vessel walls appears relatively homogeneous and closely woven. The distal ends of the vessels disappear almost imperceptibly among the alveolar elastic fibers. Proximal to this region the form and course of the vessel branching can be clearly seen.

Elastic fibers from the elastica of the blood vessels appear to be continuous with the elastica of the parenchyma, and this in turn is continuous with the elastica of the pleura (*see* below). Hence, the pulmonary elastic network appears continuous throughout. No free ends are observed except those made in preparing the blocks. This observation raises a question. If the elastic network of the pleura, blood vessels, and bronchial tree each develops independently (15), why and under what circumstances do they join?

The bronchioles are identified with aid from

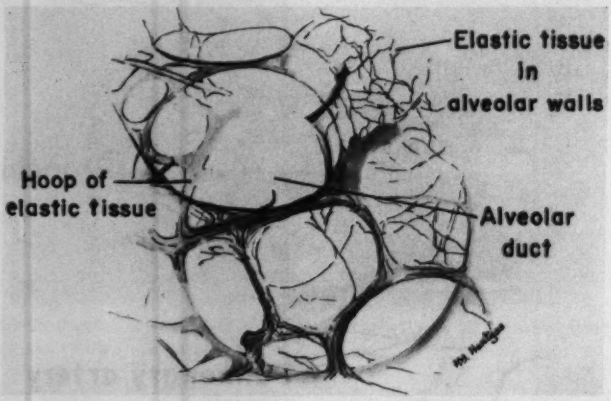

FIG. 5*A*. The pulmonary elastic fibers as shown in this drawing define an alveolar duct and the surrounding alveoli. Note the heavy strands of elastic tissue in the wall of the duct and the fine elastic strands in the alveolar walls. Formic acid corrosion preparation of a block of normal human lung. (100 ×)

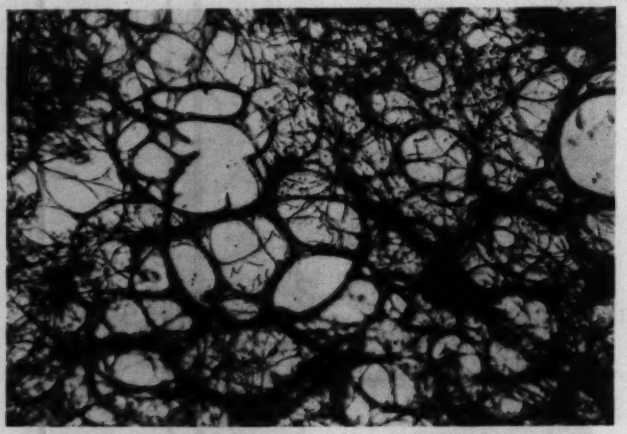

FIG. 5*B*. A photomicrograph of the same area of normal human lung as shown in figure 5*A*. An alveolar duct is outlined by heavy strands of elastic tissue. Formic acid corrosion preparation of a block of normal human lung. (100 ×)

the branches of the pulmonary artery. The mural elastic structure consists of prominent "hoops" of tissue which run obliquely around the bronchiolar wall. In the larger bronchioles (more than 200μ in diameter), longitudinal bands can be seen in addition. Both forms of bronchial elastic fibers are illustrated in figures 4*A* and *B*. The cut ends of the longitudinal fibers are clearly seen adjacent to the lumen, while the transverse hoops of elastic tissue outline the course of the tube. As the bronchiole continues, the longitudinal fibers are lost and only the circular fibers persist.

The most prominent feature of any section of lung consists of the numerous alveolar ducts. These are slightly larger than the smallest bronchioles and are defined by distinct "hoops" of elastic tissue, which themselves mark the mouths of individual alveoli. Because of the transparency and thickness of the preparation, these ducts can be followed for some distance and seem to end in clublike enlargements representing the sacculi alveolares. In figures 5*A* and *B* strands of elastic tissue can be seen defining the airway. In figures 6*A* and *B*, the elastic tissue coat of small blood vessels comes to an end near an alveolar duct.

The mouths of the alveoli themselves, therefore, are distinguished by prominent "hoops" of elastic tissue derived from the walls of the duct

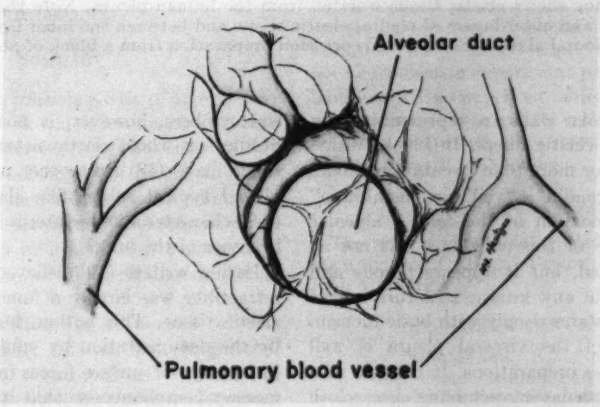

FIG. 6*A*. A drawing of an elastic network isolated from a block of normal human lung. A small alveolar duct is shown, as well as the terminal branches of two small blood vessels. (100 ×)

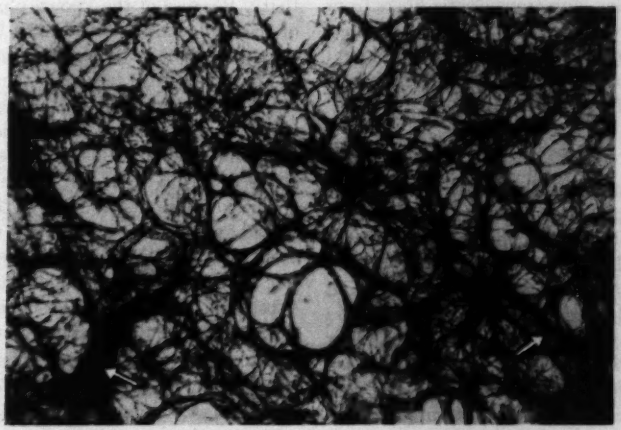

FIG. 6*B*. A photomicrograph of the same area of normal human lung as shown in figure 6*A*. Arrows identify two small blood vessels. Formic acid corrosion preparation. (100 ×)

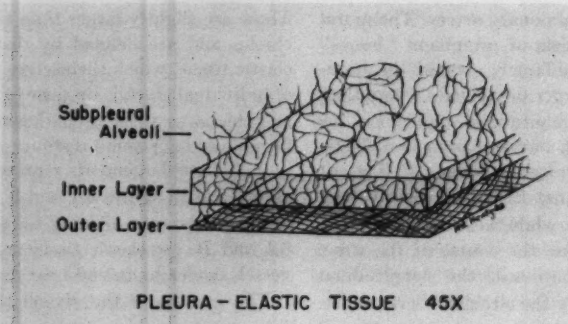

FIG. 7. A drawing shows elastic tissue isolated from the human pleura. Note the close connection between the inner and outer layers of pleural elastic tissue and between the inner layer and the elastic tissue of the subpleural alveoli. Formic acid corrosion preparation from a block of normal human lung. (80 ×)

system. The alveolar walls are represented by a network of finer elastic fibers. In blocks which have been fixed for more than twenty-four hours in 10 per cent formalin, a "veil" or "membrane" persists in the location of the former alveolar wall. The nature of this substance has not as yet been identified, but it appears porous and does not resemble any known structure in the alveolar wall. It stains deeply with basic fuchsin.

The elastica of the visceral pleura is well preserved in these preparations. It consists of a closely woven outer layer resembling cheesecloth and a somewhat looser inner layer (figure 7). In accord with observations of Miller (16) made from serial sections, numerous elastic fibers from the subpleural alveoli can be traced into the inner pleural layer and thence into the outer pleural layer. It seems plausible that these fibers might be ruptured in the formation of blebs.

DISCUSSION

What role should be assigned to the connective tissue fibers of the lung? How might this function be altered by chronic pulmonary disease? These questions have seemed important for many years, because of the abundance of collagen and elastic tissue in this organ and because these fibers are known to play a part in the physical behavior of other organs. Collagen in other sites has been shown to be strong and relatively inelastic, and there is every reason to believe it supports and limits movement of the more deformable structures of the human lung. The function of the elastic fibers, however, is not as well defined. Studies on whole elastic networks (17) and on single fibers (18) from other networks have displayed typical rubber-like elasticity. How can these characteristics be interpreted in terms of the behavior of the lung?

Earlier writers (19) believed that pulmonary retractility was largely a function of the lung's elastic tissue. This notion, however, was upset by the demonstration by von Neergaard of the importance of surface forces in determining pulmonary compliance, so that it became apparent that at least two factors operated under static conditions: surface tension and true tissue elasticity. Because of the known physical properties of elastic fibers, it seemed most likely that these were important in this latter regard.

The connective tissue of the lung may also help define the small volumes within which the surface forces work. A rich elastic tissue network surrounds each alveolus and alveolar duct and is stressed during expansion of the lung.

The intimate distribution of tissue forces generated at the lung surface is not well understood. It is at least plausible that these forces might not be distributed evenly throughout the lung substance, as they would be in homogeneous fluid medium, and that pulmonary connective tissue might be concerned in such an uneven distribution of forces. In this connection it is interesting that the pulmonary elastic fibers when relieved of surrounding supporting structures tend to retain much the same space distribution

as that found normally in the lung. How this independent configuration changes during expansion and contraction of the lung is not known but should make an interesting study.

Finally, no reliable experimental methods have been developed to affect pulmonary elastica selectively during life. Rats fed lathyrus factor show (20) consistent changes in the elastica of the media of blood vessels but not in the elastica of the lungs. Currently, intoxication with vitamin D offers promise as a method of injuring pulmonary elastic tissue (21), but its implications have not been adequately explored. Such experimental pathologic studies should be interpreted in terms of the known three-dimensional architecture of this elastic network.

Summary

The human lung consists partly of an extensive elastic tissue network which cannot be well visualized under the microscope in conventional thin sections. Corrosion of blocks of lung with warm 88 per cent formic acid will leave the pulmonary elastic network as a residue. This structure can then be embedded in gelatin and examined in three dimensions under the binocular dissecting microscope.

Blocks from the lungs of 40 normal subjects have been studied by this method. In general, the distribution of elastic tissue conforms to that previously described by the more laborious method of serial sections. This new method can be used to study natural or experimental alterations in the connective tissue of the lung.

Sumario

Aislamiento y Estudio de la Red de Tejido Elàstico del Pulmón en Tres Dimensiones

El pulmón humano consta parcialmente de una extensa red de tejido elástico que no puede visualizarse bien al microscopio en los acostumbrados cortes delgados. La corrosión de bloques de pulmón con ácido fórmico al 88 por ciento caliente deja la red elástica pulmonar en forma de residuo. Este puede luego incrustarse en gelatina y examinarse en tres dimensiones con el microscopio disecador binocular.

Con esta técnica se han estudiado bloques obtenidos de los pulmones de 40 sujetos normales. En general, la distribución del tejido elástico se conforma a la ya descrita por el método más arduo de los cortes seriados. La nueva técnica puede usarse para estudiar las alteraciones naturales o experimentales en el tejido conjuntivo del pulmón.

Resume

Isolement et étude du réseau de tissu élastique du poumon en trois dimensions

Le poumon humain consiste partiellement en un réseau de tissu élastique qui ne peut pas être bien vu au microscope, sous la forme des sections habituelles. L'attaque de blocs de poumon par de l'acide formique à 88% chaud laissera le réseau élastique pulmonaire comme résidu. Cette structure peut être enfouie dans de la gélatine et examinée en trois dimensions au microscope binoculaire disséquant.

Des blocs de poumon de 40 sujets normaux ont été étudiés par cette méthode. En général, la distribution du tissu élastique trouvée concorde avec celle décrite auparavant par la méthode plus laborieuse des coupes en séries. Cette nouvelle méthode peut être utilisée pour étudier les altérations naturelles ou expérimentales dans le tissu conjonctif du poumon.

Acknowledgment

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MULTIPLICATION OF MYCOBACTERIUM TUBERCULOSIS IN THE CORNEA AND ITS MODIFICATION BY IMMUNITY AND BY ISONIAZID[1]

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INTRODUCTION

It has previously been shown that, when *Mycobacterium tuberculosis* is inoculated into the cornea of mice, macroscopic lesions develop which attain a maximal size after three to four weeks and subsequently regress slightly (1). There is a great deal of evidence that this stabilization of the disease is due to the development of immunity (2, 3). In fact, previous immunization can cause complete or partial inhibition of the development of lesions, depending on the size of the challenge inoculum. Such an inhibition can also be produced by the administration of various chemotherapeutic substances (1, 4).

The above results have been obtained by making two types of measurement, namely, the size of the macroscopic lesion, and an estimation of the total number of organisms, i.e., viable and dead, in the cornea, involving the staining of the whole cornea by a modified Ziehl-Neelsen technique (5). This latter method will, as a rule, give results for only about one to two weeks after inoculation (unless little or no multiplication occurs), since after that time the stained mass becomes too dense to allow of any quantitative estimation.

A method has recently been developed in this laboratory for counting the total number of mycobacteria in the cornea (6, 7) and has been used, in combination with a count of living mycobacteria in the cornea, to follow in detail the course of a corneal infection and the impact of immunity and of chemotherapy upon it. By using a combination of viable and total counts, an attempt was made to follow accurately the changes in bacterial population. This was done chiefly to differentiate between a stable viable population due, on the one hand, to an arrest of multiplication, and, on the other, to a dynamic equilibrium attained when organisms are being removed, either by death or by migration, at a rate equivalent to the increase in population due to multiplication.

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MATERIALS AND METHODS

The general methods of intracorneal inoculation and vaccination with *M. tuberculosis* var. *bovis* have been described previously by Acharya, Robson, and Sullivan (3). Mice were immunized intradermally by injecting 0.01 ml. of a 10^{-3} dilution of a Dubos culture (second subculture, thirteenth day) and were challenged one month later with an undiluted Dubos culture (fifth subculture, eighth day). The organisms were passed through mice usually after seven subcultures. In this experiment, the mice were immunized with the second subculture and challenged with the fifth subculture after passage. When mice were treated with isoniazid, it was administered in the diet, 0.3 mg. of the drug being included in each 5 gm. of Medical Research Council diet 41, which is approximately the daily food intake of each mouse, i.e., a dose of 15 mg. per kg. The corneal disease was followed by the methods indicated below:

The total number of organisms in the cornea was determined by digesting the corneal structure with a mixture of collagenase and hyaluronidase. The bacteria so released were stained and then counted according to the method of Robson and Smith (6).

The number of viable organisms was determined using the method described by Knox (8). This was carried out on an aliquot of the corneal digest before carrying out the total counts.

The size of the macroscopic lesion was followed quantitatively by the method described by Rees and Robson (1) and Naguib (9).

The whole cornea was stained by a modified Ziehl-Neelsen technique (5) to estimate the size of the bacterial mass and the spread of the organisms within the cornea.

When bacterial counts were carried out, the mean result of 3 corneas was used in the first experiment and of 2 corneas in the second experiment. In both cases the corneas were selected so that their average macroscopic lesion size approximated the average lesion size of the whole group. In order to keep down contamination, 5 units of penicillin were added to each 1 ml. of collagenase–hyaluronidase in the first experiment; in the second experiment, this was used with the addition of 0.01 mg. of chlortetracycline. Various control tests showed that these agents had no significant effect on the viable counts (7).

RESULTS

Two main experiments were carried out. In the first, in which 40 mice were used, a detailed

examination of the primary infection was made. The second experiment was carried out in order to study the effect of immunity and of isoniazid. Both experiments were made on mice that had been injected intracorneally with an undiluted culture, the large inoculum being chosen since a smaller one would fall below the limit of sensitivity of the method of counting the total number of bacteria by staining.

First experiment: The results of the first experiment are shown in figure 1. The lesion size reached an average value of approximately 2.0, i.e., occupying about two-thirds of the cornea at two weeks and then remained at about this level. The total bacterial count per cornea rose for the first three to four weeks to approximately 10^7 organisms, and this number was maintained for the remainder of the experiment. The viable count followed the total count for the first two weeks, but thereafter there was a marked fall throughout the remainder of the experiment. Staining of the whole cornea by the modified Ziehl-Neelsen technique showed a gradually increasing mass of bacteria which reached the maximal value that could be quantitatively assessed (T7) at seven days.

It may be seen in figure 1 that at the start of the experiment the total count was approximately ten times the viable count, both counts being made on corneas removed immediately after inoculation. Since the stained slide on which the

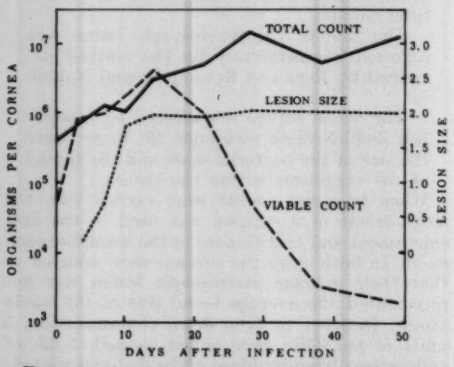

FIG. 1. Showing total number of bacteria, number of viable bacteria, and size of macroscopic lesion present in the cornea of mice inoculated intracorneally with an undiluted culture of *M. tuberculosis*. For discrepancy between total and viable counts on day of inoculation, *see* text.

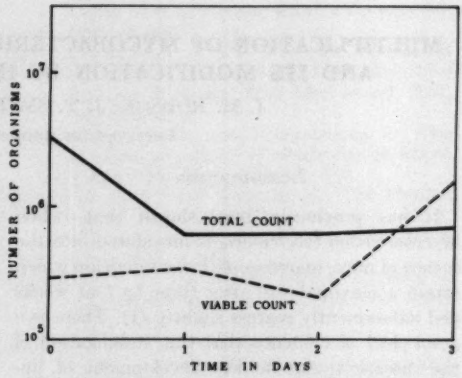

FIG. 2. Illustrating discrepancy between total and viable counts on first few days after inoculation. All mice were inoculated intracorneally with an undiluted culture of *M. tuberculosis*.

total count was made showed a good deal of clumping, the divergence appeared to be due mainly to this phenomenon, i.e., each aggregate was counted as one viable unit in the viable count, but assessed at the number of bacteria it actually contained in the total count. In the first few days following inoculation, the aggregates of bacteria in the cornea were broken up, so that a stained slide of digested cornea made some three days after inoculation contained practically no clumps. Hence, at this stage total and viable counts should be similar. In order to investigate this question further, a closer study was made of the infection over the first three days after inoculation by carrying out daily total and viable counts (figure 2). It may be seen that there was an initial fall in the total count, presumably due to escape of mycobacteria through the inoculation wound, as has been demonstrated for infections of the cornea with *M. lepraemurium* (6). At the end of three days, however, the total and viable counts were substantially the same, which is in agreement with the appearance of the stained slides in which little or no clumping was seen.

Second experiment: The second experiment was carried out in order to investigate the effect of immunity, either alone or in combination with isoniazid on corneal tuberculosis. The combined treatment was used to see whether isoniazid would enhance the effect of immunity. Four groups of 30 mice each were used. Two of these (groups 2 and 4) had been immunized one month

previously. All animals were injected intracorneally with an undiluted culture of *M. tuberculosis*. The groups were as follows:

1. Nonimmunized group, untreated (control)
2. Immunized group, untreated (vaccinated)
3. Nonimmunized group treated with isoniazid from time of infection until end of experiment (isoniazid)
4. Immunized group treated with isoniazid from time of challenge infection until end of experiment (vaccinated and isoniazid-treated)

The results are shown in figures 3, 4 and 5.

It may be seen that in the control group (figure 3) the results were very similar to those obtained in the first experiment. The longer duration of this second experiment showed clearly that the decline in the viable count at first took place very rapidly, but after about five weeks the slope of the curve changed and the fall in the viable count became much slower. The results for the vaccinated animals (figure 3) showed important differences from those in the control mice. The total count did not show the marked initial rise (as in the controls) but, in fact there was some fall which was presumably due to loss of mycobacteria through the injection wound. The viable count, too, showed practically no increase and, allowing for the declumping described above, the actual number

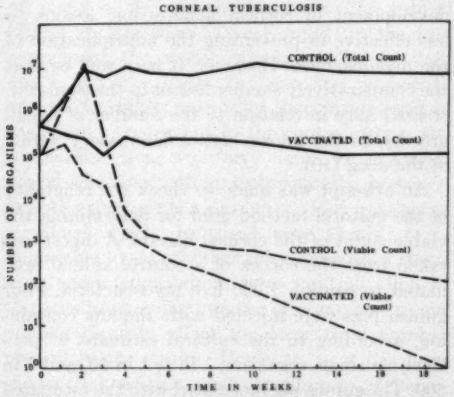

FIG. 3. Showing the effect of previous vaccination on total number of bacteria and number of viable bacteria in cornea of mice inoculated intracorneally with an undiluted culture of *M. tuberculosis*.

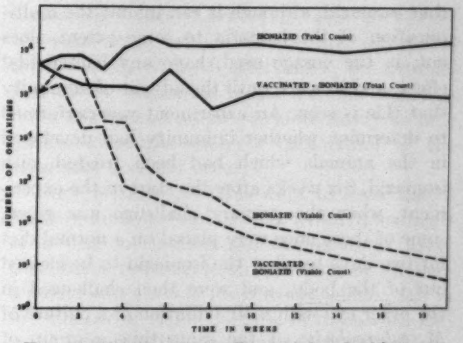

FIG. 4. Showing the effect of isoniazid treatment either alone or in combination with previous vaccination on total number of bacteria and number of viable bacteria in cornea of mice inoculated intracorneally with an undiluted culture of *M. tuberculosis*.

of viable bacteria probably started to decline quite early in the experiment, at first rapidly and later on more slowly. Thus, it can be said that the immunity resulting from previous vaccination produced an immediate bacteriostatic and bactericidal effect. The dual effect was evidenced by the fact that the viable count gradually decreased almost from the beginning, yet there was no increase in the total number of bacteria (viable and dead) within the cornea. This dual effect was not seen in the control group until two weeks after infection, i.e., a period which allowed for the development of immunity, as shown by previous work (5). It is noteworthy that in both control and vaccinated groups the viable count at first fell rapidly and later much more slowly, and it is puzzling that the inflexion in the curve occurred in both cases some five weeks after the corneal inoculation (primary or challenge inoculation).

The results for the animals previously vaccinated and treated with isoniazid (figure 4) were similar to those obtained in vaccinated mice (without drug treatment), and this will be discussed later. In the nonimmunized mice treated with isoniazid (figure 4), the results were qualitatively similar to those seen in the control group. Thus the viable count increased somewhat, though to a lesser extent, during the first two weeks after infection, and then fell at first rapidly and then more slowly. The total count showed some increase at first and stabilized after about four weeks. This would suggest

that isoniazid, although it can inhibit the multiplication of the bacteria to some extent, does not, in the dosage used, have any bactericidal effect, and it is not until the advent of immunity that this is seen. An experiment was performed to determine whether immunity had developed in the animals which had been treated with isoniazid. Six weeks after the start of the experiment, when the primary challenge was given, some of these mice were placed on a normal diet for two days to allow the isoniazid to be cleared out of the body, and were then challenged in the other eye with a 10^{-3} dilution of a culture of *M. tuberculosis*; at the same time a group of normal mice were similarly inoculated. These latter mice all developed corneal lesions in the expected manner while no lesions developed in the mice previously treated with isoniazid, showing that immunity was indeed present. The small corneal lesions present in the isoniazid-treated group showed no increase in size after withdrawal of the drug, suggesting that the stabilization of the lesion (and of the total bacterial population) was due to the influence of immunity.

The macroscopic lesions in the four groups of animals of the second experiment are shown in figure 5. The lesions in all of the treated groups were much smaller than in the controls, with no significant differences between them. Since the bacterial population was larger in the isoniazid-treated mice than in those previously immunized (whether treated with isoniazid or not), the results with the macroscopic lesion sizes were unexpected and were therefore further analyzed.

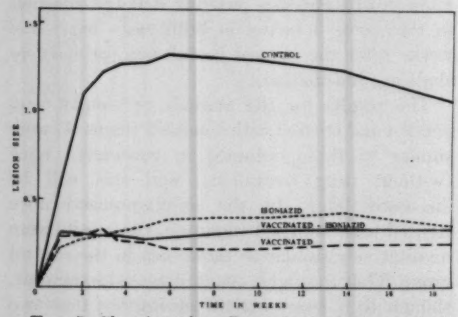

FIG. 5. Showing the effect of previous vaccination, of isoniazid treatment, and of both on the development of macroscopic lesions in corneas of mice inoculated intracorneally with an undiluted culture of *M. tuberculosis*.

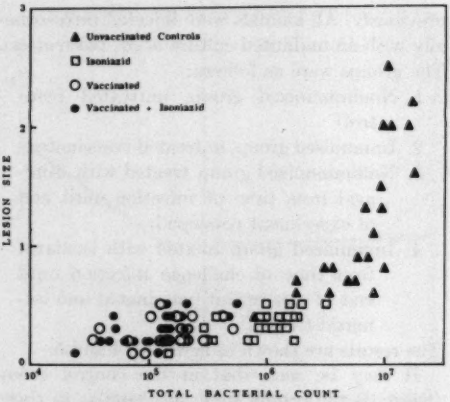

FIG. 6. Showing relation between total bacterial content and size of lesion in various groups of mice inoculated intracorneally with an undiluted culture of *M. tuberculosis*. Each point represents the total bacterial count and the lesion size for a single cornea. The mice were killed at various periods after inoculation.

In figure 6 the total bacterial population per cornea is plotted against lesion size for all animals of the four groups. As expected, the control animals had larger lesions and more bacteria in the corneas. The isoniazid-treated animals, although their lesions were no larger than in the immunized mice, formed a separate group with a higher bacterial content. This confirms the conclusion that isoniazid treatment, although as effective as immunity in keeping down the development of corneal macroscopic lesions, is less effective in preventing the multiplication of the mycobacteria. However, it may well be that the comparatively smaller lesions in the isoniazid-treated mice in relation to the number of bacilli are due to the known anti-inflammatory action of the drug (10).

An attempt was made to check the reliability of the cultural method used for determining the viable count of the corneal digests. A digest was taken from the cornea of a control animal estimated to contain 1,000 live mycobacteria. Four guinea pigs were injected with aliquots containing, according to the cultural estimate, respectively: a single organism, 1 in 5, 1 in 50, and 1 in 500. The guinea pig inoculated with the estimated organisms ultimately died from generalized tuberculosis, whereas the other 3 animals developed no such infection. It is realized that such a small experiment has limitations but, neverthe-

less, the results suggest that the viable count obtained with the method used is not grossly different from one based on the ability of the mycobacteria to kill guinea pigs.

Discussion

These experiments show that, when a comparatively large inoculum of *M. tuberculosis* (between 10^5 and 10^6 organisms) is injected into the cornea of mice, multiplication of these organisms rapidly occurs, reaching a maximal number some two weeks after inoculation. The macroscopic lesion which begins to appear after the latent period of a few days also increases rapidly in size to reach a maximum at about the same time as the viable count, i.e., some two weeks after inoculation. This seems to be a turning point in the development of the local disease since: there is a stabilization in the size of the macroscopic lesion, there is no further significant increase in the total number of mycobacteria, and there is a sudden and dramatic fall in the number of viable mycobacteria within the cornea. Moreover, it may be concluded that, after the first fortnight, no marked multiplication of mycobacteria occurs; otherwise the total number in the cornea would increase, as clearance from the cornea occurs at a very slow rate (2).

These results suggest that after a fortnight there is a bacteriostatic effect which prevents any appreciable multiplication of the organisms and also a bactericidal effect which rapidly kills off many of the organisms present. The rate of killing at this stage is very rapid: in the first experiment the viable population fell by half every fifty-five hours between the fourteenth and thirty-eighth days after inoculation; and in the second experiment in the control group, the comparable time was forty hours for a similar period after inoculation. Subsequently, however, in both experiments a residue of viable organisms remained which decreased very slowly. It is impossible to say whether this represents a static or dynamic equilibrium, since multiplication of this small remaining number of organisms would not significantly affect the large total number present in the cornea. However, as it has been shown that, when a small inoculum of *M. tuberculosis* is injected into the cornea of previously vaccinated mice, no appreciable multiplication occurs (2), it is believed that the first possibility, i.e., a static equilibrium, is the more likely. It is noteworthy that Lurie (11) has previously observed that, when rabbits are inoculated intravenously with *M. tuberculosis*, the destruction of the organisms in the various organs is rapid at first and progresses more slowly as time passes, although complete elimination of the organisms does not occur.

There is much previous work to show that a marked immunity can develop within a fortnight of corneal inoculation (3), and it seems likely that this is responsible for the onset of the bactericidal effect which leads to the sudden fall in the number of viable bacteria in the cornea and to an arrest in the development of the macroscopic lesion. The results obtained in mice which were vaccinated one month before intracorneal inoculation are in keeping with such an interpretation. In these mice, there was no multiplication of the mycobacteria within the cornea from the very beginning, since the total number did not rise and, moreover, the number of viable organisms began to decrease rapidly at a very early stage after inoculation. These effects, i.e., fall in viable population and no increase in total population, are the same as those seen with a delay of fourteen days after the start of the infection in mice which had not been vaccinated previously. The effects are in keeping with the view that the changes in bacterial population which occur after about a fortnight in animals not previously vaccinated are, in fact, due to the development of immunity.

The rate of killing in the vaccinated group was such that over a period of twenty-eight days after challenge the viable population fell by a half every eighty-two hours, assuming the viable count to be the same as the total count on the day of the challenge infection. This was about half the rate at which the organisms died in both experiments on unvaccinated mice. Thus, it seems that the effect of immunity was not identical in these two groups, i.e., the previously vaccinated and those not previously vaccinated. There are at least two possible explanations for the difference in the rate at which the organisms are killed. One is that the multiplication which occurs in the cornea of unvaccinated mice stimulates the production of a higher degree of immunity than is attained from vaccination by intradermal inoculation. The rate of multiplication of mycobacteria inoculated into the skin of mice is being investigated in this

laboratory in order to see whether the results would fit in with such an explanation. Another possible explanation is that immunity can kill organisms more rapidly which have recently undergone marked multiplication in the cornea than organisms which have newly been injected after multiplication *in vitro*. It is well known that organisms in the logarithmic phase of growth are especially susceptible to adverse conditions (12). A similar phenomenon was observed by Lurie (11), who found that immunity in rabbits destroyed large numbers of *M. tuberculosis* more rapidly than smaller numbers.

The results in the animals treated with isoniazid also need consideration. They show that the drug was able to prevent any marked multiplication of the mycobacteria in the cornea and that the population of viable organisms remained stable for about a fortnight after inoculation. The effectiveness of the drug treatment under these conditions was, therefore, less marked than that of immunity, which not only prevented bacterial multiplication, but also rapidly killed off many of the organisms. After a fortnight, however, the number of viable organisms in the isoniazid-treated animals also rapidly began to fall in exactly the same way as in animals not treated with isoniazid. This suggests that this fall was due to the development of immunity and, in fact, it was shown by a suitable challenge in the other eye that treatment with isoniazid did not prevent the development of immunity in these animals.

The finding that a combination of immunity and isoniazid did not produce a more marked effect than immunity alone is not unexpected. It is well known that isoniazid produces its most marked effects on dividing mycobacteria and that it is relatively ineffective on bacteria in the resting stage (13). Since immunity by itself largely, if not completely, arrests mycobacterial multiplication under the conditions of the present experiments, it cannot be expected that isoniazid would be able to contribute appreciably to the rate at which the bacteria are killed in the cornea.

In the discussion so far, it has been assumed that the turning point in the corneal disease which occurs about a fortnight after inoculation is due to the immunity which has developed during this period. In fact, it is known that immunity develops almost from the time of inoculation and that some degree of immunity can be demonstrated in animals challenged two days after inoculation (3). It might well be asked, therefore, why no effective evidence of this immunity was seen in the present study for some two weeks, at which time there was the sudden bactericidal effect. A possible explanation is that a lethal effect on the mycobacteria occurs only when a certain level of immunity has been reached, in the same way as a certain threshold level of chemotherapeutic substances, e.g., isoniazid, will markedly affect the bacteria while a level below this threshold will have little or no effect. Thus, when the threshold level of immunity has been reached, the organisms are rapidly killed off to give the steep part of the descending curve of the viable count. Why this process does not proceed to a complete elimination of all of the viable organisms in the cornea—but stops to leave a residual population which subsequently decreases only very slowly—is unknown. It is tempting to assume, however, that this residue is resistant to the bactericidal effect of immunity, either through a process of adaptation or, from the very first, as part of a heterogenous population with different degrees of resistance to immunity. This question is being further investigated.

Summary

The multiplication of *M. tuberculosis* in the mouse cornea was studied by doing total and viable counts on the bacteria released by enzymatic destruction of the cornea.

For about a fortnight after inoculation, *M. tuberculosis* multiplied in the cornea, and macroscopic lesions developed. During this period the total and viable counts were very similar. The disease was then stabilized by immunity which produced both a bacteriostatic and bactericidal effect. The viable count fell dramatically, but later the fall became much slower.

Immunization of the mice one month before intracorneal inoculation completely inhibited multiplication of the bacteria, and there was also an immediate bactericidal effect, so that the viable count fell from the time of inoculation.

Isoniazid (15 mg. per kg.) had a moderate bacteriostatic effect, but as immunity developed this produced the typical actions described above. Isoniazid treatment did not enhance the effect of immunity in previously vaccinated mice.

Sumario

Multiplicación del Mycobacterium Tuberculosis en la Córnea y su Modificación por la Inmunidad y la Isoniacida

Practicando numeraciones totales y viables en las bacterias liberadas por la destrucción enzimática de la córnea, se estudió la multiplicación del *M. tuberculosis* en la córnea murina.

Aproximadamente durante la quincena consecutiva a la inoculación, el *M. tuberculosis* se multiplicó en la córnea, formándose lesiones macroscópicas. Durante este período, las numeraciones totales y viables fueron muy semejantes. La enfermedad se estabilizó entonces por virtud de la inmunidad que produjo efecto tanto bacteriostático como bactericida. La numeración de bacilos viables bajó teatralmente, pero después la baja se volvió mucho más lenta.

La inmunización de los ratones un mes antes de la inoculación intracorneal inhibió totalmente la multiplicación de las bacterias, y hubo además inmediato efecto bactericida, de modo que la numeración de microbios viables bajó desde el momento de la inoculación.

La isoniacida (15 mg./kg.) ejerció moderado efecto bacteriostático, pero a medida que se formaba inmunidad, ésta produjo los precitados efectos típicos. La isoniacidoterapia no acrecentó el efecto de la inmunidad en los ratones vacunados anteriormente.

Resume

Multiplication du Mycobacterium tuberculosis dans la cornée et ses modifications par l'immunité et l'isoniazide

La multiplication du *M. tuberculosis* dans la cornée de la souris a été étudiée en faisant les calculs totaux et "vivants" des bactéries libérées par destruction enzymatique de la cornée.

A peu près une quinzaine de jours après l'inoculation, les *M. tuberculosis* se multiplièrent dans la cornée et des lésions macroscopiques se développèrent. Pendant ce temps, les calculs totaux et "vivants" furent très semblables. La maladie fut ensuite stabilisée par l'immunité qui produisit un effet à la fois bactériostatique et bactéricide. Les calculs "vivants" tombèrent d'une façon impressionnante, mais par la suite, la chute se ralentit.

L'immunisation des souris un mois avant l'inoculation intracornéenne inhiba complètement la multiplication des bactéries et il y eut aussi un effet bactericide immédiat, de sorte que le compte "vivant" décrut à partir du moment de l'inoculation.

L'isoniazide (15 mg/kg) eut un effet bactériostatique modéré, mais, au fur et à mesure que l'immunité se développa, il se produisit les réactions typiques ci-dessus décrites. Le traitement par l'isoniazide n'exagèra pas l'effet de l'immunité chez les souris préalablement vaccinées.

Acknowledgment

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L VARIATION IN MYCOBACTERIA[1,2]

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INTRODUCTION

The bacterial forms known as L variants have been cultured from many genera, but none have been reported as occurring in mycobacteria. This paper summarizes a four-year investigation of Mycobacterium species, testing their ability to produce L forms under varied conditions.

The subject of L forms in mycobacteria has especial interest because some investigators now believe the atypical structures observed *in vivo* since 1883 (1) may be stages of the L cycle. Therefore, it is important that L growth be studied if the atypical form is to be cultured from infected tissue and its reversion to the distinctive acid-fast rod facilitated.

Interest in virulence of L variants has been raised by Rubio-Huertos (2), who found that *Clostridium tetani* produces an L variant more toxic than the bacillary form.

The demonstration of L variation in mycobacteria brings to a conclusion the extensive controversy concerning filtrability of tubercle bacilli (3–6). It is recognized that L variants have minute particles capable of initiating growth. Thus, without resort to filters, L colonies demonstrated filtrability.

MATERIALS AND METHODS

Organisms:

Mycobacterium tuberculosis var. *hominis*. Six strains had been grown *in vitro* for one month only; a seventh, No. 879, had been transferred twice before storage at 6°C. for eighteen months. These strains of *M. tuberculosis* were from patients with pulmonary tuberculosis.

Mycobacterium tuberculosis var. *hominis* H37Ra.

BCG.

Mycobacterium avium ATTC 11755.

Mycobacterium smegmatis.

Inducing agents: To produce L variation, the following specific bacterial inhibitors were tested: Penicillin G, known as benzathine penicillin G,[3] dihydrostreptomycin, sulfadiazine, sulfadiazine combined with penicillin, and isoniazid. The benzathine penicillin G was used by: incorporation in the medium to give a desired concentration; and dropping on the surface of the agar either directly or impregnated in a filter-paper disc.

When benzathine penicillin G was used with dihydrostreptomycin, a filter-paper strip saturated with one antimicrobial was placed above the medium on one side and the second antimicrobial was placed in filter paper in a parallel line on the opposite side of the medium. Employing antimicrobials follows the original observation of Pierce that L variants are drug resistant (7).

Synthetic medium:

Glucose	0.15%
Sodium lactate	2.0%
K_2HPO_4	0.9%
Nicotinamide	1 γ/ml.
Salts	0.2%
Casamino acids, vitamin free	0.5%
Agar, Noble's or purified[4] (Difco)	0.8%

The salt mixture contains:

$MgSO_4 \cdot 7H_2O$	40 gm.
NaCl	2 gm.
$FeSO_4 \cdot 7H_2O$	2 gm.
$MnSO_4 \cdot 4H_2O$	8 gm.

The following were autoclaved individually: nicotinamide and glucose in a 10 per cent solution. The agar and sucrose were autoclaved together in a double-strength solution. The salt, phosphate buffer, and casamino acids were homogenized by prolonged grinding, dissolved in distilled water in double strength, and filtered through a Seitz apparatus. The sodium lactate was also filtered with this mixture. The pH of this medium was 7.0 to 7.2.

Media with peptone base included the following:

PPLO agar

Thioglycollate medium (Brewer's anaerobic agar)

Nutrient agar constituted from nutrient broth[4] plus 0.8 per cent agar. If not specified, this was Difco granular agar. In later work, Noble's agar[4] or purified agar[4] were employed. This is referred to as medium No. 3.

Tryptose agar.

Hypertonicity was obtained by increasing the

[1] Publication No. 55 of the Biology Department of Wayne State University, Detroit, Michigan.

[2] Supported in part by Grant E-921 of the Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

[3] Combined dibenzylethylenediamine dipenicillin G, procaine penicillin G, and potassium penicillin G, manufactured by Wyeth Laboratories, Inc.

[4] Manufactured by Difco Corporation.

electrolyte concentration or by adding sucrose or maltose. For high electrolyte medium the sodium chloride was increased to 0.5 M, as suggested by Sharp (8) and by Bonifas (9) who noted that strains within a species might vary in their need for hypertonic milieu.

High sucrose has been employed to grow L variants of enterobacteriaceae (10, 11) and was used here in 0.35 M or 0.7 M concentration.

Serum enrichment consisted of human, horse, or guinea pig serum incorporated in concentrations from 1 to 40 per cent, with inactivation at 56°C. when the concentration was more than 1 per cent. Improved growth has been observed of L variants of Proteus and Salmonella strains with inactivated sera, while Smith and Morton (12) have shown that sera have heat-labile inhibitors for PPLO. PPLO serum fraction,[4] a lipoprotein concentrate from horse serum, was used in numerous studies.

pH gradient plates: To test the role of hydrogen ion in the L cycle, medium was prepared according to the description of Sachs (13). Square plastic Petri dishes were used for media of pH 6.0 and pH 8.0, the plates being slanted during the hardening of the first layer. A pH differential existed along the face of the medium one hour after preparation.

The medium for pH gradient plates consisted of nutrient broth, 0.8 per cent; agar,[4] 0.8 per cent; horse serum, 20 per cent, inactivated; and sodium chloride or sucrose as stated.

Inoculation of cultures: Cultures made by the pour-plate method were compared with duplicates on which the inoculum was streaked over the surface.

Organisms for inocula varied in age from one to fourteen days. Strain No. 879 was also tested as an aged culture. *M. avium* and *M. smegmatis* were grown on nutrient agar slants or Petragnani's medium. Other species were harvested exclusively from Petragnani's medium.

Replicate plates, in which colonies were transferred from the entire surface of a plate, were made by pressing the initial culture with a velvet pad which was then stamped onto the fresh medium (14).

Incubation atmosphere: Anaerobic tests employed Fortner's method (15). Increased carbon dioxide tension was obtained by a candle jar.

Stains: Usually Dienes' stain (16), methylene blue and azure II, was employed. For visualizing the exceedingly fine filaments of L growth with phase contrast, Sabin's (17) vital stain, neutral red and janus green, was dried on a coverslip which was then placed over a wet mount.

Results

Basic essentials for L growth: Early experimentation produced L bodies only, which did not undergo further development. They were produced in the diffusion zone bordering high concentrations of penicillin and usually were of giant dimensions, measuring to 50μ. The large spheres were frequently ruptured with extruded contents visible in the medium. A giant L body of *M. tuberculosis* is shown in figure 1.

Many modifications in the culture method did not result in continuation of the L cycle. No improvement resulted when the pH was varied from 5.0 to 9.0. Addition of human, horse, or guinea pig serum or PPLO serum fraction in concentrations from 1 to 40 per cent were ineffective, as were anaerobiosis and increased carbon dioxide tension. There was little difference between the media tested: PPLO agar, tryptose agar, and Brewer's anaerobic agar. Thus it became evident that methods adequate for L development in Proteus species (18, 19) were inadequate for the L cycle in mycobacteria.

Using media made hypertonic by the addition of sodium chloride resulted in sporadic positive findings; L colonies appeared in the diffusion zone of penicillin, but results were not reproducible. It was interesting to note that, in the presence of sodium chloride, L bodies had prolonged viability, as indicated by reversion to acid-fast bacilli in *M. smegmatis*. Reversion often was initiated in the naked cytoplasm which had poured from the sphere, and rods gradually filled the entire L body. When L colonies did develop, they were of the same type as those seen with sucrose (described below). At times the growth rapidly lysed when the cultures were opened and exposed to the atmosphere.

Sucrose as a stabilizing agent proved the necessary factor for consistently obtaining L

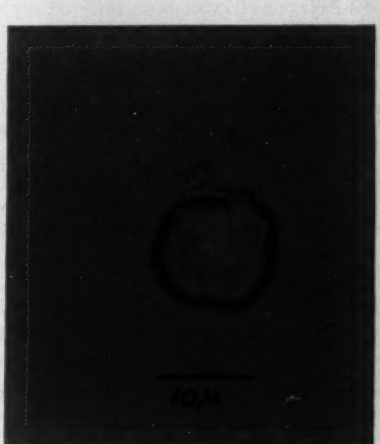


FIG. 1. L body of *M. tuberculosis* var. *hominis*. Membrane has absorbed Sabin's vital stain.

growth with either the synthetic medium or with nutrient agar (medium No. 3). Unexpectedly, when fastidious species were tested, they developed rapidly but exclusively as L colonies, and no antimicrobial was required (table 1).

Effect of antimicrobial drugs upon L growth: Penicillin, in exceedingly high concentration, was a provocative agent initiating the L cycle in situations in which otherwise no L growth was found. On media in which L growth occurred spontaneously, penicillin resulted in larger L colonies and sometimes altered the appearance of the L forms (table 2).

Morphology of L growth: To aid in interpreting the photomicrographs, a schematic drawing of the L cycle is given (figure 2). Initially a central swelling appears in a bacterium, enlarging until the cell is spherical and thus constitutes the "L body." An L body may either revert to the bacterial form or continue the L stage by extension of filaments of variable diameter. It is the growth of these mycelia which results in L colonies. L growth of mycobacteria was of several types:

Rectangles of subsurface material, easily overlooked as artifacts, appeared refractile by

TABLE 1

L Forms from Mycobacteria

	Hypertonic Sucrose in Media*
M. tuberculosis (*hominis*) No. 879	L colonies exclusively
M. tuberculosis (*hominis*) No. 879, aged culture	
24 hours:	No growth
48 hours:	L colonies only, in areas with moderate inoculum.
	Pigmented bacillary colonies, *non*acid fast, in heavily inoculated areas. Some colonies are mixed bacillary and L growth.
M. tuberculosis H37Ra	L colonies only
BCG	L colonies
	Small L bodies (protoplasts?)
	Acid-fast cocci
M. avium	L colonies only
M. smegmatis	Normal colonies only unless antimicrobial employed.

* Synthetic medium and "nutrient agar" gave similar findings. All readings were made after 24 hours except for aged strain No. 879.

TABLE 2

Effect of Antimicrobial Drugs upon L Growth

M. tuberculosis H37Ra No. 879 (*hominis*) BCG	Penicillin: Highest concentration Inhibits all growth, including L colonies
	Lesser concentrations Stimulate L growth. May alter L colony morphology
M. avium	Isoniazid: High concentrations alter L colony morphology, giving vacuolated colonies.
	Dihydrostreptomycin High concentrations inhibit L growth
M. smegmatis	Penicillin: High concentrations give giant L bodies which gradually fill with acid-fast rods

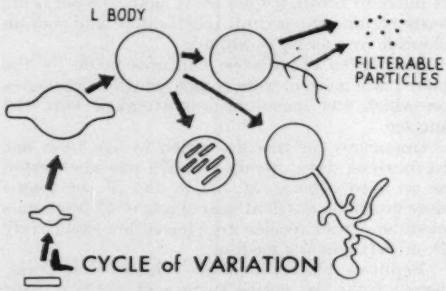


Fig. 2. Schematic drawing of the L cycle.

low magnification. Vital dyes applied above these colonies penetrate slowly, and staining was evident only after several hours. Such deep growth broke through the surface at points, resulting in bacillary or L colonies on the agar. An anastomosing group of such deep colonies with foci of surface L growth is shown in figures 3 and 5. When the submerged growth is examined with phase optics, it appears as in figure 4. At times such growth, consisting of very fine strands with interspersed swellings, may be initiated and will remain on the agar. For reference we shall call this colony the "fungoid" type.

Another common form of L growth consists of wide hyphae with moderate swellings at intervals (figure 6). Due to their irregular surface when viewed with low magnification,

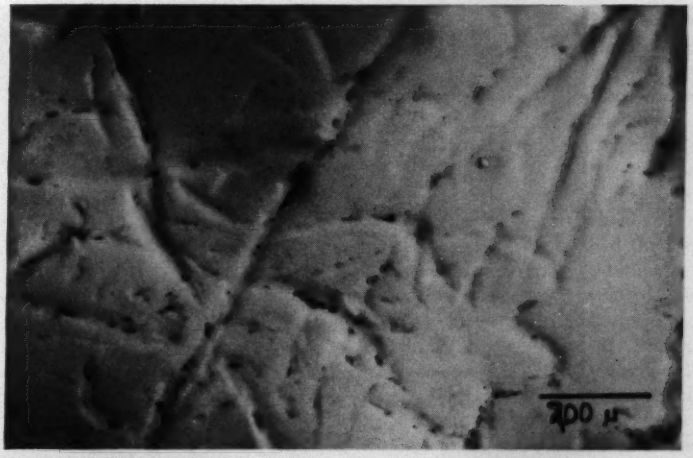


FIG. 3. Ramifying deep growth of BCG, breaking through the surface at intervals. Superficial colonies are stained with Dienes' method.

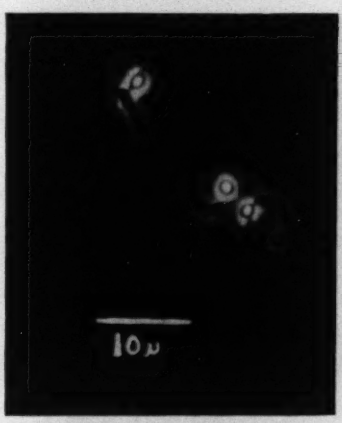


FIG. 4. Mount of submerged growth from figure 3. Phase contrast.

such colonies are referred to as "granular." Such wide hyphae were often observed developing from protoplasts (figures 7 and 8). Mixed colonies of the fungoid and granular growth were frequent, showing transitions from fine to wide hyphae.

The third type of colony possesses the large vesicles found in classical L colonies of other genera. These have been most successfully produced on synthetic medium near the combined antimicrobials penicillin and dihydrostreptomycin, but have also resulted from the action of penicillin alone and from isoniazid.

Not all L growth could be classified as a distinct colony type. For such an atypical example, see figures 9 and 10.

Conditions modifying L growth: Growth of L forms occurred with varied nutrition, but not with equal success. The need for increasing or maintaining a given tonicity was well established. Sodium chloride was inferior to sucrose for such a purpose, giving L forms only in the diffusion zone of 15,000 to 30,000 units of benzathine penicillin G.

For all strains, L forms grew more rapidly in the anaerobic portions of the culture, with a tendency to appear subsurface even when inoculation had been superficial. An anaerobic atmosphere did not alter this situation, indicating that the physical state, as well as oxygen tension of the medium, may be involved.

Carbon dioxide added to the atmosphere did not improve L growth, but aerobic culturing was in closed containers which resulted in some carbon dioxide accumulation.

Nutritional requirements of L variants are modest, as the synthetic type of medium demonstrates. Thus amino acids may function as the nitrogen source; nicotinamide alone satisfied the vitamin requirement.

Vitamin-free medium also supported L growth of all of the Mycobacterium strains, as shown by tests in which the nicotinamide was omitted from the synthetic medium. However, the slow rate of growth of the L colonies indicated that nicotinamide greatly fosters L growth, although it is not an absolute requirement.

Since serum is not needed in the synthetic medium, its role in natural medium must be not

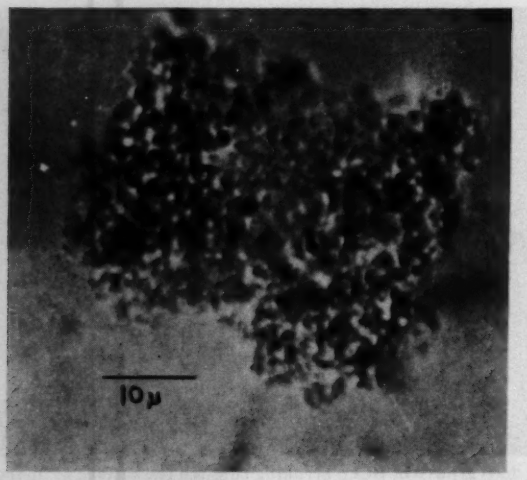


FIG. 5. BCG higher magnification of surface growth shown in figure 3.

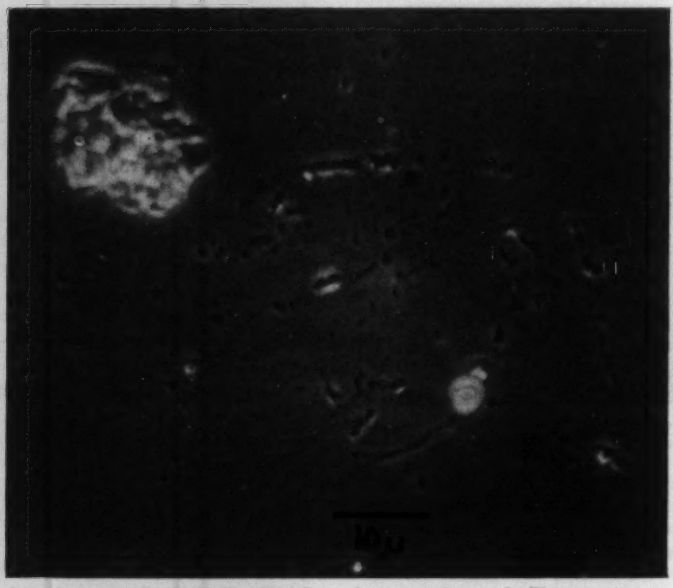


FIG. 6. *M. tuberculosis* var. *hominis*, No. 879. Granular type of growth. Phase contrast.

for nutrition but rather to detoxify some inhibitory substance. That serum is not essential for growth, but rather neutralizes substances in standard medium, has been shown for Proteus by Medill and O'Kane (20).

Noble's agar and purified agar gave essentially similar growth of L forms and were superior to standard granular agar.

The age of culture used for inoculum was not a critical factor, as is true in Salmonella (18) and Proteus (21). Cultures varying in age from one to fourteen days gave no appreciable difference in number or morphology of L forms. When a twenty-four-hour culture of *M. tuberculosis* var. *hominis* was compared with organisms of the same strain but which had been refrigerated

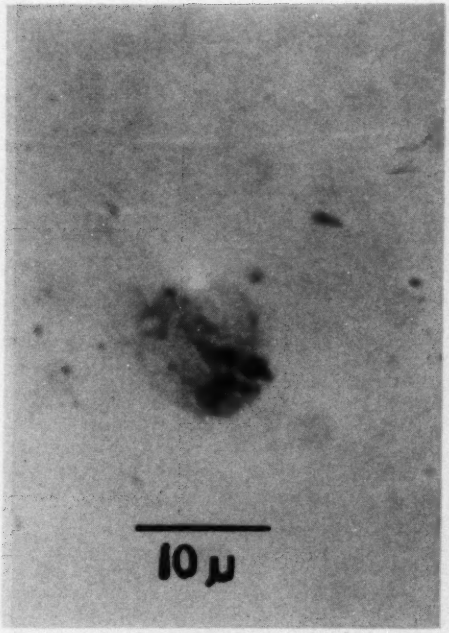


FIG. 7. *M. tuberculosis* var. *hominis*. Ziehl-Neelsen stain. Protoplast. Not acid fast. Synthetic medium with no serum.

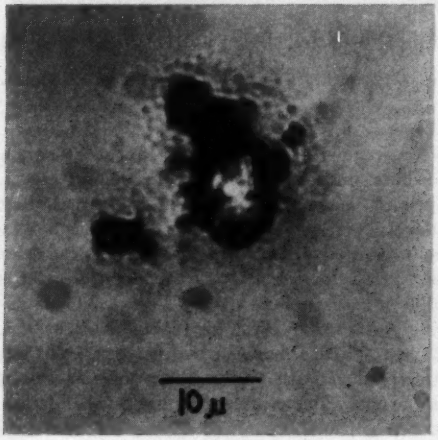


FIG. 8. *M. avium*. Enlarging protoplast. Ziehl-Neelsen stain. Central portion is acid fast.

eighteen months, identical L growth appeared from the aged bacilli after a lag period of only two days (*see* table 1).

Horse serum added to "nutrient agar" enhanced the growth of the L variants of all of the strains and was adequate in a concentration as low as 1 per cent. Guinea pig serum was equally satisfactory. Human serum was inferior.

The pH gradient plates showed L colonies restricted to a narrow zone whenever the medium was inferior. Such a strict pH dependence resulted when impurities were in agar, when human serum was present, or when sodium chloride rather than sucrose furnished the hypertonicity. Likewise, it has been noted that L colonies of Salmonella grow over a wide pH range only if the medium is optimal (22).

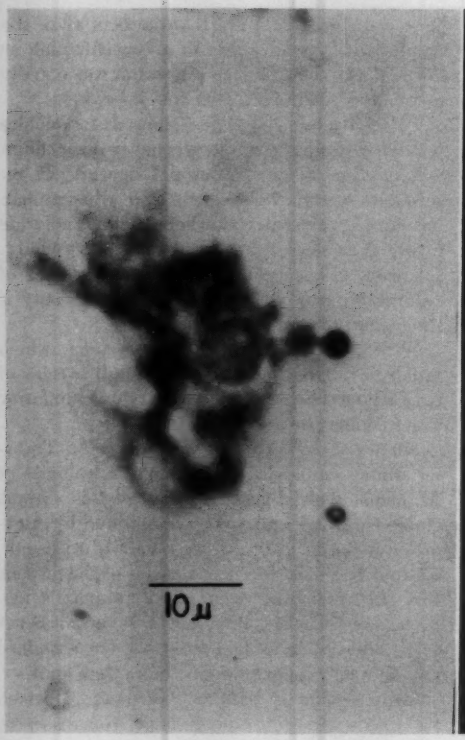
With the exception of *M. smegmatis*, which rapidly reverted to acid-fast rods, all species of mycobacteria behaved with remarkable similarity when comparisons were made.

Studies of reversion of L forms to bacilli: Transfer studies employing the granular L colonies of *M. avium* showed great stability of this variant (table 3). Chick embryo extract, found by Alexander-Jackson (23) to foster reversion to bacilli, was not beneficial in the conditions of the present test. Reversion did occur on Petragnani's medium, but the exact nutrition for reversion is yet to be defined; as table 3 indicates, one standard medium may foster reversion more than another.

Examination of clinical material: Thirteen specimens of cerebrospinal fluid from cases of tuberculous meningitis, when examined with phase optics, showed forms which resembled the fungoid and granular types of L colonies (figure 11). Ziehl-Neelsen stains revealed nonacid-fast colonies, with acid-fast bacilli forming in the center or growing at the edge from nonacid-fast mycelia. L bodies, or protoplasts, were seen in several preparations. Likewise, sputum from patients with pulmonary tuberculosis showed, in addition to acid-fast bacilli, granular-type L colonies with acid-fast bacilli growing from them. The prevalence of these forms, especially in the cerebrospinal fluid, suggests that fluorescent antibody might give a rapid and definite identification. The problem is complicated by the ubiquitous nature of granular L colonies. Alexander-Jackson (23) has noted that such forms, resembling the nonacid-fast stage of tubercle bacilli, are found on glassware and in distilled water, in most instances representing variants of diphtheroids.

DISCUSSION

The L variation in mycobacteria illustrates many interesting aspects of the L cycle. Remark-



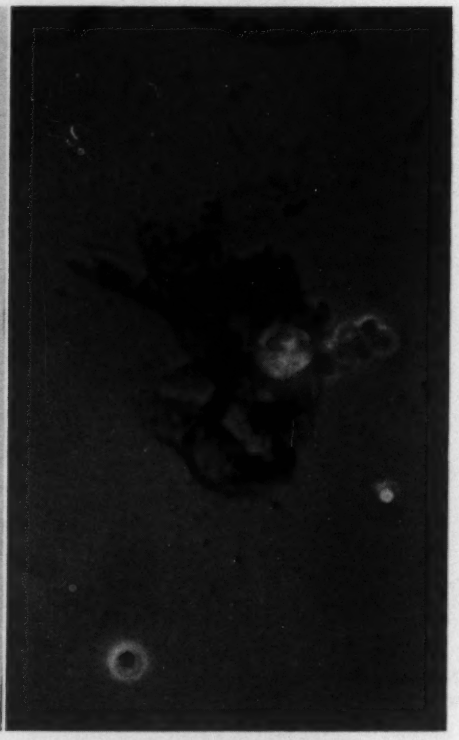


FIG. 9 (Left). Ziehl-Neelsen stain—no acid-fast growth. Central L body has grown by both budding and by a meshwork of hyphae. Synthetic medium.

FIG. 10 (Right). Same field as figure 7. Phase contrast. Structure is better defined. Two smaller L bodies with halo are also seen.

able is the giant L body which may attain a diameter of 100 to 150μ, developing from a single rod. Freundt (24) has observed large spheres in the PPLO, noting that they only occur on inferior medum, do not undergo further development, and thus might be regarded as irreversibly damaged cells. In more solid medium, the findings indicate that giant L bodies sometimes are capable of reversion to the bacterial form, as occurred with *M. smegmatis*. Giant L forms have also been observed in this laboratory in cultures of staphylococci (25), anaerobic staphylococci,[5] and PPLO strains, constituting a point in favor of the view that *L* forms and PPLO are identical.

Not only giant L bodies but smaller spheres were frequently seen in the mycobacteria in medium unsuitable for continuation of the L cycle. It is strongly debated at present whether such L bodies should be called protoplasts. The cultures in this laboratory have given information pertinent to answering this question, as the following discussion shows. Protoplasts extensively studied by Weibull (26) and others (27, 28) are spherical bodies resulting when cell walls are digested with *lysozyme*. Protoplasts are of uniform size, have internal granules which stain, and have not been found capable of continued reproduction. On the other hand, bodies which appear similar, produced by *antimicrobial* action, have been capable of continuing growth as L forms (10, 11).

In the experience of the present writers, L bodies are of extremely varied size, depending

[5] Peptococci, Bergey's *Manual of Determinative Bacteriology*, 1957.

TABLE 3

TRANSFER STUDIES, L COLONIES OF M. AVIUM

	Resultant Growth at 4 Weeks
Media Which Did Not Give Reversion	
Multiple granular L colonies transferred to:	
Nutrient agar with 10% horse serum	L colonies only (granular)
Synthetic medium with 0.35 M sucrose, 1% horse serum, 1% chick embryo extract (replica plate)	L colonies only (granular)
Synthetic medium as above, without sucrose (replica plate)	L colonies only (granular)
Media Permitting Reversion	
Large granular colonies transferred to:	
Petragnani's slants	Acid-fast bacilli
Löwenstein's slants	Rods with typical morphology for bacillary stage of *M. avium*, but not acid fast.
Small granular colonies transferred to:	
Petragnani's slants	Acid-fast bacilli, some encased in giant L bodies. The peripheral membrane of the L body is not acid fast.
Löwenstein's slants	Typical acid-fast bacilli

upon medium and provocative stimulus. In most stages the L body reveals no structure with vital stains. Thus, there is basis for saying that the terms protoplast and L body should not be employed interchangeably. However, penicillin, under some conditions, does produce bodies of uniform size, definite membrane, and internal granules which stain. Therefore, it seems that among the varied L bodies made by penicillin some are protoplasts. Antimicrobial drugs have been seen to produce structures which resemble protoplasts in Proteus, Salmonella, and Mycobacterium. It is of interest here that phage-produced protoplasts in mycobacteria have also been observed (29).

No antimicrobial agent is required to produce L

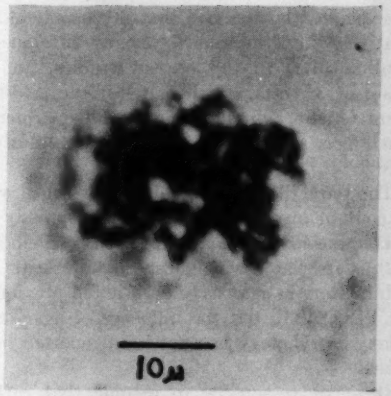


FIG. 11. Cerebrospinal fluid in tuberculous meningitis. Ziehl-Neelsen stain. Phase contrast. Slender hyphae in center of colony are acid fast.

growth if nutrients essential for the bacterial stage are omitted from the medium; the mycobacteria then appear exclusively as L variants. However, an especially large inoculum supplies growth factors (*see* table 1). When numerous aged tubercle bacilli were placed on a deficient medium, bacillary growth appeared in some areas of the culture, although the organisms proved nonacid fast. All duplicate cultures with only moderate inocula gave L growth only. Staphylococci and streptococci exhibit the same characteristic of appearing in the L form on vitamin-deficient medium (25).

The morphology of the L growth was found to be related to both medium composition and specific inhibitors. The classic L colony, vacuolated as a result of large swellings along hyphae, occurs only in response to a potent provocative agent, or conversely in medium exceptionally free of substances which inhibit L growth. A strong inducing agent has most frequently been supplied by a high concentration of penicillin. The same provocative agent, used in lower dosage, results in thicker hyphae with only small swellings, giving the granular colony. Factors influencing the morphology of L growth have been elucidated by studies of Salmonella (18, 30), and it was apparent that the same principles applied in mycobacteria.

The classic L colony, always described as vacuolated or vesiculated, is the most difficult to initiate in any genus. It is exceedingly difficult to produce in the mycobacteria. This may well

be explained by the fact that mycobacteria are relatively impermeable to agents in aqueous solution (31). In the present studies, an old strain of *M. avis*, which had lost the acid-fast characteristic, produced vesiculated colonies much more easily than an acid-fast strain of *M. avis*.

The refractile areas in cultures, which proved to contain mycobacterial L growth, grossly resemble the PPLO colonies reported by Sheppard (32) as associated with nonspecific urethritis.

Inhibitors in agar have been noted previously for PPLO (33), but the influence of agar on L colony morphology has not been reported heretofore.

It seems reasonable to assume that certain stages of the L cycle constitute Much's granules (34) and other atypical forms noted *in vivo* or in culture (35). Together, the fungoidal and granular types of colonies resemble the growth earlier described as the "zoological form" in mycobacteria observed in tuberculous cerebrospinal fluid and in slide cultures by Alexander-Jackson (23). She suggested that the colonies might be the L forms of Dienes as reported for other bacteria. It is the conclusion of the present writers, from comparing Mycobacterium variants with L variants of 35 strains of Proteus and 110 strains of Salmonella, that the Mycobacterium variants are L forms. They are difficult to see since they favor the deep fungoidal L colony more than do variants of other bacteria. They are also difficult to identify because of the small size of the elements in a *Mycobacterium L* colony. Their structure can usually be delineated only with phase optics; they are miniature replicas of L colonies as seen in other genera.

Summary

Mycobacterium L colonies developed rapidly on several simple media. Their growth was fostered by sucrose, which is known to stabilize L forms, and was inhibited by some types of agar and excess serum.

In media lacking the essential nutrients for acid-fastness, the L phase grew exclusively; on complete media the L and bacillary stages grew together. For all of the species investigated, *M. tuberculosis*, *M. smegmatis*, and *M. avis*, L growth appeared as a physiologic process, not requiring specific inhibitors. However, certain antimicrobials stimulated the L growth.

The L cycle in mycobacteria is the same as that shown in other genera of bacteria and thus provides a new basis for the filtrability of this genus.

The L colonies were often numerous in known tuberculous cerebrospinal fluids which did not show acid-fast rods in smears.

Sumario

La Variación L en las Micobacterias

En varios medios sencillos se formaron rápidamente colonias del *Mycobacterium L*. Fomentó su proliferación la sucrosa, que, según se sabe, estabiliza las formas L, inhibiéndola algunas formas de agar y exceso de suero.

En medios carentes de los principios nutrientes indispensables para la ácidorresistencia, la fase L se desarrolló exclusivamente; en medios completos, proliferaron juntas las fases L y las bacilares. En todas las especies investigadas, *M. tuberculosis*, *M. smegmatis* y *M. avis*, la proliferación L apareció en forma de proceso fisiológico, sin requerir inhibidores específicos. No obstante, ciertos antimicrobianos excitaron la proliferación L.

En las micobacterias, el ciclo L es idéntico al desplegado en otros géneros de bacterias, suministrando así una nueva base para la filtrabilidad de este género.

Resume

Variation L chez les Mycobactéries

Des colonies de Mycobactéries L se developpèrent rapidement sur plusieurs milieux simples. Leur dèveloppement fut aidé par du sucrose, qui l'on sait, stabilise les formes L, et fut inhibé par certains types d'agar-agar et l'excès de sérum.

Dans des milieux dépourvus des éléments nutritifs essentiels pour bacilles acido-résistants, la phase L poussa en exclusivité; dans les milieux completés, les stades L et bacilliformes poussèrent ensemble. Pour toutes les espèces étudiées, *M. tuberculosis*, *M. smegmatis*, et *M. avis*, le développement de L apparut être un processus physiologique, ne demandant pas d'inhibiterurs spécifiques. Cependant, certains agents antimicrobiens stimulèrent le développement de la phase L.

Le cycle L, chez les mycobactéries, est le même que celui montré dans d'autres genres de bactéries et ce fait produit ainsi une base nouvelle pour la filtrabilité de ce genre.

Les colonies L furent souvent nombreuses dans des liquides cephalorachidiens avérés tuberculeux mais qui ne montraient pas de bâtonnets acidorésistants sur les lames.

Acknowledgments

The writers thank Harold Rossmoore and Emma Armonath for valuable suggestions, and Norma Broom for her cooperation throughout the course of this study. They are greatly indebted to

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A COMPARATIVE STUDY OF THE CAUSATIVE AGENT OF A MYCOBACTERIAL DISEASE OF SALMONOID FISHES[1]

II. A Description of the Histopathology of the Disease in Chinook Salmon (*Oncorhynchus Tshawytscha*) and a Comparison of the Staining Characteristics of the Fish Disease with Leprosy and Human Tuberculosis

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Introduction

In the past there has been speculation as to the relationship between the acid-fast bacilli of a disease in fish, usually referred to as "fish tuberculosis," and similar bacilli from leprosy and tuberculosis in humans. Layman (1) traced the historical pattern of leprosy among people on islands and along the banks of rivers and lakes in endemic areas and correlated it with the practice of eating raw or poorly prepared, supposedly diseased, fish products. Recent investigators[2] have commented on the parallel existing between the organisms of the two diseases in relation to their culturability. A third parallel exists: the difficulty of staining either of the organisms in fixed, routinely treated tissue sections. To be sure, other similarities do exist—both organisms are acid fast, both are mycobacteria, and both are pathogens—but these characteristics are shared in common with other organisms such as tubercle bacilli. The possibility that the bacilli from leprosy and tuberculosis were the same, or closely related, stimulated the present investigation.

The relationship to tuberculosis, as previously noted, was immediately apparent when a disease caused by an acid-fast bacillus was first noted in fish. This theory was the factor that stimulated experimental studies attempting to show a causal as well as a casual relationship between the human and fish pathogens (2). The results of these experiments were inconclusive and controversial, with the consequence that the present state of knowledge concerning the relationship between these diseases is confused and limited.

Another aspect concerning the fish disease in relation to human diseases is the possible relationship of the unclassified mycobacteria that infect man and the acid-fast bacilli of fish and other cold-blooded animals. One organism from fish has been identified as the same species of Mycobacterium that was originally isolated and identified from a cold abcess in a human (3). This does not mean to imply that fish organisms necessarily would be pathogenic for man nor would the reverse infection necessarily occur, but the possibility does exist. There are other factors that support the hypothesis of a human pathogen being of a cold-blooded animal origin. Many unclassified organisms are cultivated at temperatures lower than are the typical human pathogens. Many unclassified organisms are nonpathogenic for guinea pigs, hamsters, and mice. Pigmentation and colony morphology among the cultures of unclassified human isolates vary (4, 5). All of this is true for acid-fast organisms in fish. It has been pointed out that all previous attempts to adapt the warm- or cold-blooded organisms to the opposite group have resulted in inconclusive data. In the present investigation, data have been obtained that could be used as a basis for further studies of the relationship of organisms from cold-blooded animals—specifically the fish—with organisms from warm-blooded animals.

In an earlier paper (6), one of the writers discussed the staining characteristics of the mycobacterial disease in fish, and brought out the fact that the method of staining greatly influenced the success or failure of demonstrating the presence of acid-fast bacilli in tissue sections. It was also shown that, when used in this laboratory, the Fite-Faraco method of treating prepared tissue sections was much superior to the Ziehl-Neelsen method for staining acid-fast organisms in fish tissue. In addition, a comparison was made of the staining of the organism of human tuberculosis with the organisms in diseased, adult and juvenile, chinook salmon (*Oncorhynchus tshawytscha*). The present report offers data obtained from a comparison of the organisms causing

[1] From the Western Fish Disease Laboratory, U. S. Fish and Wildlife Service, Sand Point Naval Air Station, Seattle, Washington.

[2] Personal communications.

the disease in two age groups of salmon with the organism causing the disease of leprosy in humans.

Brief descriptions of a mycobacterial disease in salmon were given in previous papers (2, 6); however, they were too inadequate to be considered definitive. Earlier investigators have described diseased conditions caused by acid-fast organisms in fresh- and salt-water fish. Johnstone (7) reported a disease in cod (*Gadus morhua*) in which the infection was primarily limited to the skin, and an inflammatory reaction was observed. Aronson (8) described a condition that was similar to that observed in the salmon, but the description was not adequate to afford a careful comparison. Johnstone's (9) description of the condition in a halibut (*Hippoglossus hippoglossus*) indicated a granulomatous inflammation in which there were very few organisms. The disease as seen in neon tetras (*Hyphessobrycon inessi*) by Nigrelli (10) again elicited an inflammatory response by the fish. Unfortunately, these descriptions were also inadequate for a systematic comparative study with the disease observed in salmon.

The present report will describe in detail the disease seen in salmon, discuss its manifestations, and briefly compare it with other fish and human diseases. It is hoped that future descriptions of diseases due to acid-fast bacilli in fish will permit additional comparisons so that the confusion and omissions that exist concerning the disease in cold-blooded animals can be eliminated and real progress can be made to elicit a better understanding of the disease as an entity and as a possible evolutionary link in the acid-fast bacilli–disease chain.

Materials and Methods

A detailed discussion of materials and methods was given in the initial paper dealing with the staining characteristics of the fish acid-fast organism (6). The following is a brief account of the procedures used in the present study:

Materials: Whole fish and tissue fragments of adult and juvenile chinook salmon were the sources of the acid-fast bacilli of fish, and sections of human lung and ear lobe provided the bacilli of the human diseases; all were preserved in 10 per cent formalin.[3]

Methods: For the Ziehl-Neelsen acid-fast studies, the slides were prepared in the usual routine method and brought up through the deparaffinization and hydration stages. At this point the tissues were pretreated with absolute alcohol, glycerol, 6 per cent sulfuric acid, a combination of these, or were not pretreated. The tissues were then stained in cold carbolfuchsin, destained by 1 per cent hydrochloric acid or 3 per cent sulfuric acid, and the usual routine followed from this point. The Fite-Faraco acid-fast studies followed the same routine except that the tissues were deparaffinized in a 1:2 mixture of mineral oil and xylene. All tissues studied for histopathology were prepared in the routine manner and stained by the Harris hematoxylin-eosin method according to the Armed Forces Institute of Pathology manual.[4] The protocols and experimental design used in this study are listed in tables 1 and 2.

Results

Histopathology

Juvenile salmon tissue: The disease in juvenile salmon was characterized by a massive infection which primarily involved the connective and adipose tissue surrounding the intestinal tract. The lesions contained brightly acid-fast bacilli occurring in tremendous numbers and forming broad bands or layers around the intestinal tract and adjoining viscera (figure 1). In hematoxylin and eosin–stained sections the lesions appeared as acellular, homogenous, dull blue zones (figure 2). The single organ most affected was the pancreas. In a severe infection, the pancreatic acinar tissue, which was scattered in the visceral adipose tissue, was virtually destroyed. The organism appears to have no specific affinity for pancreatic cells, however, and their destruction is probably secondary to the invasion of the surrounding tissues.

The most striking characteristic of the disease is the almost complete absence of a cellular response to the bacterial invasion. In both early infections in which few organisms were present, and in the later infections in which great masses of acid-fast bacilli surrounded the viscera, there was no inflammation. As the disease progressed, massive clumps of bacteria were invested by a thin wall of fibrin, but few or no inflammatory cells were seen (figure 3).

The distribution of the organisms was variable. By far the great majority occupied the visceral adipose tissue. Small concentrations were also seen on occasion, however, in the hematopoietic tissue of the kidney and in the spleen and liver. In each of these sites the organisms were usually intracellular, indicating that they had been

[3] The writers wish to express their appreciation to Dr. G. L. Fite, Chief, Laboratory Branch, U. S. Public Health Service Hospital, Carville, Louisiana, for providing tissue containing leprosy bacilli.

[4] *Manual of Histologic and Special Staining Technics*, Armed Forces Institute of Pathology, Washington, D. C., 1957.

TABLE 1

PROTOCOLS EMPLOYED FOR THE TREATMENT OF PREPARED SLIDES

Ziehl-Neelsen Method	Fite-Faraco Method	Harris Hematoxylin Stain
1. Deparaffinize and hydrate	1. Deparaffinize in a 1:2 mixture of mineral oil and xylene	1. Deparaffinize and hydrate
2. Wash well in running tap water	2. Blot dry and then wash under tap water	2. Wash well in running tap water
3. Pretreat,* if any, and wash	3. Pretreat,* if any, and wash again	3. Follow the routine as listed in the Armed Forces Institute of Pathology *Manual of Histologic and Special Staining*§ for the Harris hematoxylin stain
4. Stain† in cold carbolfuchsin	4. Stain† in cold carbolfuchsin	
5. Destain‡	5. Destain‡	
6. Wash in running tap water	6. Wash in running tap water	
7. Dehydrate through 95 per cent alcohol	7. Counterstain with 0.1 per cent methylene blue	
8. Counterstain with 0.1 per cent methylene blue	8. Blot and air dry	
9. Dehydrate, clear, and mount	9. Mount	

* Pretreatment: a) absolute alcohol, b) glycerol, c) 6 per cent sulfuric acid.
† Stain: 10 ml. 10 per cent alcoholic basic fuchsin in 100 ml. of 5 per cent aqueous phenol.
‡ Destain: a) 1 per cent alcoholic hydrochloric acid, b) 3 per cent aqueous sulfuric acid.
§ *Manual of Histologic and Special Staining Technics*, Armed Forces Institute of Pathology, Washington, D. C., 1957, pp. 32-35.

engulfed by fixed macrophages and had then proliferated. Rarely, the ventral body wall had a focus of organisms in the anal area (figure 4). This material was heavily infected in the specimens examined which contained remnants of yolk. Indeed, the great concentrations of organisms followed the anatomic distribution of yolk so closely as to suggest this as the primary site of infection.

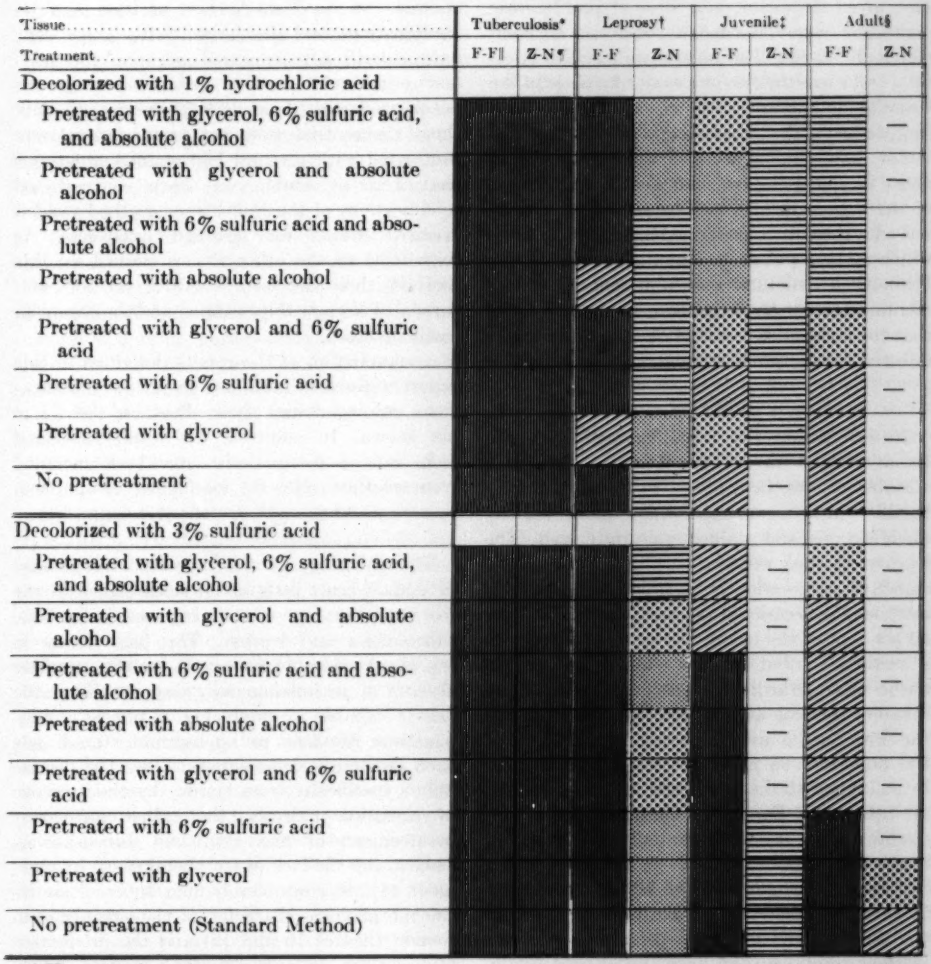
The gills, central nervous system, and renal tissue of the kidney were not involved in the young fish examined. Infection of the digestive tract was usually limited to the serosal covering. In fact, no extensive involvement of the digestive mucosa was observed in any fish.

Adult salmon tissue: The disease in the older age groups appeared to be merely an extension of that observed in the juveniles. The minute foci of organisms seen in the kidneys, spleen, and liver of the young fish were replaced by massive lesions in the adults. In contrast, the great concentrations of bacilli surrounding the intestinal tract had virtually disappeared, leaving large areas of caseous necrosis with only occasional organisms. The adults, in addition, showed an extension of the disease to formerly unaffected areas. These included the gills, heart, and renal tissue. The central nervous tissue of the adults was not examined.

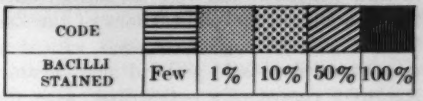
Severe damage to the spleen, liver, and kidney was observed. In general, the lesions were characterized by massive concentrations of organisms which had infiltrated and proliferated unchecked by inflammatory response. In the spleen, large epithelioid cells were clustered around concentrations of organisms which appeared to be proliferating intracellularly (figures 5 and 6). In the liver (figure 9) and in the hematopoietic tissue of the kidney, the parenchymal cells were invaded and destroyed. In the kidney, the spread of organisms was usually much greater, and large areas of caseous necrosis were formed (figures 7 and 8). The renal elements of the kidney are apparently involved secondarily to the destruction of the surrounding hematopoietic tissue. In large areas of caseation, the tubules and glomeruli were destroyed. In some areas not directly invaded with bacteria, however, the basement membranes of the glomerular capillaries showed marked thickening, possibly indicating primary damage.

Even in the adults, the gill tissue was involved only to a minor degree. The most common site of organisms was the capillaries of the lamellae which project from the gill filaments. Foci of bacteria were usually located at the proximal end of these capillaries at the base of the lamellae, but occasionally they were found at the distal tips. There was no cellular reaction to these organisms.

TABLE 2



* Human tuberculous tissue
† Human leprous tissue
‡ Juvenile chinook salmon tissue
§ Adult chinook salmon tissue
‖ Fite-Faraco method
¶ Ziehl-Neelsen method



Small foci of organisms were also found in the heart muscle, but the degree of involvement was minor. The muscle wall of the abdomen was the site of rather large abscess-like lesions. The bacilli destroyed muscular tissue but did not infiltrate the surrounding areas widely, thus producing a circumscribed lesion (figure 13).

The lesions in the connective tissue surrounding the intestinal tract were exceptional in that the disease appeared to be under some degree of control and in a stage of regression. The large masses of organisms were no longer present; in their former site, areas of caseation are now found (figure 14), delineated by a thin band of

fibrin. Only occasional organisms were seen in such areas. However, new sites of proliferating organisms were occasionally seen in adjacent pancreatic tissue. The muscle wall of the intestinal tract was the site of a major increase in the eosinophilic granule cells which are a normal component of the submucosal area (11).

The immature ovaries of these fish showed many degenerating ova, but an actual infection of the eggs with acid-fast bacteria was not observed. These ova contained acid-fast globules which stained yellow in hematoxylin and eosin. While such structures may represent a developmental stage of the organism, it appears likely that the material is ceroid (12). Mature ova from infected fish were not studied.

Staining

Human tissue: The bacilli in leprous human tissue stained in all modifications but with variable results, in contrast to human tubercle bacilli which were apparently unaffected by modifications and stained uniformly well. The leprosy bacillus stained very poorly with the standard and variously modified Ziehl-Neelsen methods. An occasional bacillus, to approximately 10 per cent of the bacilli known to be present in a section, showed staining. This same human tissue was markedly and adversely affected by absolute alcohol and glycerol modifications of the Fite-Faraco method. Only 50 per cent of the organisms in a section were demonstrated by staining with these two modifications, whereas all other Fite-Faraco methods, standard and modifications, stained essentially 100 per cent of the bacilli.

Juvenile salmon tissue: The acid-fast organisms in juvenile tissue stained better than those in the adult tissue, but were considerably poorer in their reactions than were the leprosy bacilli. Sections stained by modifications of the Ziehl-Neelsen method and decolorized with 1 per cent hydrochloric acid revealed more organisms and were consistently better than were those stained with modified Ziehl-Neelsen methods and decolorized with 3 per cent sulfuric acid. Decolorization with 3 per cent sulfuric acid seemed better than decolorization with 1 per cent hydrochloric acid as part of the Fite-Faraco technique. The former method obtained results that were 50 to 100 per cent successful, and the organisms were darker in color and more distinct and easily observed in sections.

Adult salmon tissue: All adult salmon tissue stained by the Ziehl-Neelsen method and its modifications and decolorized with 1 per cent hydrochloric acid appeared negative for acid-fast organisms. In the Ziehl-Neelsen groups decolorized with 3 per cent sulfuric acid, only those tissues that were not pretreated or were pretreated with glycerol had stained organisms that were detectable. In sharp contrast, all modifications of the Fite-Faraco method yielded positive results for acid-fast organisms. As with most of the other tissues stained by this method, those decolorized with 3 per cent sulfuric acid were readily scanned and the organism easily detected.

A compilation of the results described in this report is given in table 2. The various modifications employed and their effect on the tissue are shown. In addition, the results obtained from human tuberculosis have been included from another paper (6) for further comparison.

Discussion

The pathology of the mycobacterial disease in salmon bears little or no resemblance to the two important mycobacterial diseases in humans, tuberculosis and leprosy. The fish disease is sharply demarcated from both by the complete absence of an inflammatory response. That the fish is capable of producing a typical granulomatous response to appropriate stimuli has been previously demonstrated (13). The disease differs specifically from leprosy by the presence of caseation necrosis, the rather infrequent involvement of the skin and subcutaneous tissues, and the lack of peripheral nerve involvement (4). It resembles human tuberculosis by the morphologic character of the organisms in section (figures 10 and 12) and the production of caseation necrosis. The fish disease differs by the absence of tubercle formation and by the difference in tissue susceptibility. The respiratory system is practically unaffected, although the gills are in many ways homologous to lungs. In contrast, the spleen and liver are the sites of progressive infection, which is not usually the case in tuberculosis in humans (15). The hematopoietic tissue of both fish and humans may be the site of a progressive infection.

The complete absence of an inflammatory response suggests the possibility that the young fish are infected through the ova with a resulting "fetal tolerance" to the organism. The distribu-

tion of the bacilli also suggests that the initial contact may be through the yolk sac material. The absence of a cellular reaction deserves further study. Also unexplained is the regression of the peri-intestinal lesions. This conceivably could be correlated with an antibacterial product produced by the increased numbers of acidophils of the intestinal tract wall. Such an hypothesis, however, appears incompatible with the unchecked lesions in other organs.

The disease in no way resembles other known bacterial diseases of fish. The various gill diseases are characterized by hyperplasia and inflammation (16). Kidney disease is manifested by an extensive, chronic, granulomatous, inflammatory response with caseation (17). "Cold-water disease" is an acute septicemic infection which includes primary involvement of the renal glomeruli (18).

Variable results were obtained when fixed sections of adult and juvenile chinook salmon were stained to detect the presence of acid-fast bacilli. The results obtained indicate that the age of the fish, the treatment of the tissue, and the method of staining all influence the ability of the organism to take up stain. The poor staining results obtained from fixed adult chinook tissue as compared with those from fixed juvenile chinook tissue may reflect the action of the former tissue on the organism. It has been noted that in the adult fish there may be a decrease in numbers of acid-fast bacilli in specific areas or organs, an alteration of their predominant foci in these sites as compared with juvenile tissue, or an increase in the numbers of acidophils in areas of adult tissue. These changes or the unknown initiators of these changes may be sufficient to alter the physical and/or chemical composition of the remaining bacilli, thus rendering them less susceptible to stains. However, differences within groups of juvenile or adult tissue have not followed a predictable pattern, so that the above-cited possibilities and others will require concentrated investigation before a final lucid explanation can be offered.

Without question, the Fite-Faraco method proved to be the best method for staining the bacilli observed in tissue of salmonoid fishes. The results were all positive, to a varying degree, and the bacilli usually stained a uniformly bright to deep red color. A slight modification of the original method—the use of 3 per cent sulfuric acid for decolorizing and 0.1 per cent methylene blue for counterstaining—is the method now used routinely in this laboratory.

The Ziehl-Neelsen method proved to be unsatisfactory when used in this laboratory, and is no longer employed for staining prepared sections. The difference in results obtained by the two methods is illustrated in figures 17 and 18. A mass of organisms on the periphery of the liver stained by the Fite-Faraco method is shown in figure 17. The same tissue stained by the Ziehl-Neelsen method is displayed in figure 18. It is apparent by observing the few organisms detectable in the latter figure how poorly the stain is taken up by the organisms.

The variable staining of the human leprous tissue, as shown in table 2, was not surprising. The long history of difficult staining within prepared tissue of this organism was the reason for the development of the Fite-Faraco method. The results of this investigation merely substantiated previous findings. The investigation of the acid-fast organism in salmonoid tissue was stimulated by the possibility that it and the leprosy bacillus might be the same or similar because of the difficulty of demonstrating either of them in preserved tissue. However, a careful comparison of organisms, their staining reactions, the histopathology of their diseases, and the fact that the fish pathogen can be cultured with difficulty tend to eliminate such a possibility at present. Further morphologic, serologic and, when possible, biochemical studies must be made in order to fully establish the relationship between the two organisms.

Because of the lack of these basic comparative characteristics in the pathology of the disease and in the morphology and staining characteristics of the acid-fast organisms of fish as compared with those of human tuberculosis and leprosy, it is suggested that the name of the disease be changed from "fish tuberculosis," a misnomer, to "fish mycobacteriosis." The first person to report on a disease in fish caused by an acid-fast bacillus (19) erroneously labeled the disease "tuberculosis," probably because of the staining characteristics of the organisms. This name has been used since that time. The name "leprosy" could have been applied as readily because of the similarity of equally superficial characteristics, such as geographic distribution, the difficulty of staining, and the difficulty of culturing both the fish and human

pathogens. "Fish leprosy" would have been as applicable and as inaccurate a name as "fish tuberculosis." The present choice suggested for the name of the disease has been substantiated by the recent identification of the organisms from salmonoids and neon tetras (3, 20) and by previous identifications in other fishes (8, 21–23). The proposed name would have a more universal application to the conditions observed in various fishes and would be less misleading to future students of the disease.

Summary

The staining characteristics of acid-fast bacilli causing a disease in chinook salmon (*Oncorhynchus tshawytscha*) have been compared with the staining characteristics of the acid-fast bacilli causing leprosy in humans. Both organisms are difficult to stain in prepared tissue sections. The Fite-Faraco method appears to be the method of choice for staining either bacilli in tissue. There does not appear to be any other basis for equating the two organisms by staining characteristics.

The histopathology of the disease in juvenile and adult chinook salmon has been described. The outstanding characteristic of the disease is a complete lack of an inflammatory response to the organism. The pathology of the disease bears virtually no resemblance to that observed in leprosy, and only a superficial similarity exists with tuberculosis in humans. The pathology of the disease in salmon does not appear to be similar to the pathology described for other fresh- and salt-water fishes.

It is suggested that the name of the disease be changed from "fish tuberculosis" to "fish mycobacteriosis," because of a lack of basic, comparative characteristics of the pathology and organisms of the disease. This name is in agreement with the identification of the organism from various fishes.

Sumario

Estudio Comparativo del Agente Etiológico de una Enfermedad Micobacteriana de los Peces Salmonoides. II. Descripción de la Histopatología de la Enfermedad en el Salmón "Quinnat" (Oncorhynchus tshawytscha) y Comparación de las Características Colorantes de la Enfermedad de los Peces con las de la Lepra y la Tuberculosis Humana

Se comparan las características colorantes de los bacilos ácidorresistentes que ocasionan una enfermedad en el salmón "quinnat" (*Oncorhynchus tshawytscha*) con las de los bacilos ácidorresistentes que ocasionan lepra en los seres humanos. En ambos casos, resulta difícil la coloración en cortes histológicos preparados. El método de Fite-Faraco parece ser el de elección con ambas clases de bacilos en los tejidos. No parece que haya ninguna otra base para equiparar los dos microbios por sus características colorantes.

Se describe la histopatología de la enfermedad en el salmón "quinnat" juvenil y el adulto. La característica sobresaliente de la dolencia es la carencia total de respuesta inflamatoria al microbio. La anatomía patológica de la afección no guarda virtualmente la menor semejanza con la observada en la lepra y no existe más que similaridad superficial con la de la tuberculosis humana. En el salmón, la histopatología no parece ser semjante a la discrita para otros peces de agua dulce o salada.

Debido a la falta de características comparativas fundamentales en la histopatología y los microbios patógenos, propónese que se cambie el nombre de la enfermedad de "tuberculosis" a "micobacteriosis" de los peces. Este nombre concuerda con la identificación del microbio en varios peces.

Resume

Une étude comparée de l'agent responsable de la maladie mycobactérienne des Poissons Salmonidés. II. Une description de l'histopathologie de la maladie chez le Sauman "chinook" (Oncorhynchus tsawytscha) et une comparaison des caractéristiques de coloration dans la maladie du poisson, la lèpre et la tuberculose humaine

Les propriétés de coloration des bacilles acidorésistants causant une maladie chez le saumon "chinook" (*Oncorhynchus tshawytscha*) ont été comparées avec celles des bacilles acidorésistants causant la lèpre chez les humains. Ces deux organismes sont difficiles à colorer dans les préparations de coupes de tissu. La méthode de Fite-Faraco semble être la méthode de choix pour les colorer tous les deux dans les tissus. Il ne semble pas qu'il y ait d'autre base de comparaison entre ces deux organismes en ce qui concerne leurs propriétés de coloration.

L'histopathologie de la maladie a été décrite chez la saumon "chinook" jeune et adulte. Le caractère le plus remarquable de la maladie est le manque complet de réponse inflammatoire au germe. La pathologie de la maladie ne comporte virtuellement aucune ressemblance avec celle observée dans la lèpre, et il existe seulement une ressemblance superficielle avec la tuberculose des humains. La pathologie de la maladie chez le saumon ne semble pas être semblable à celle dé-

crite chez d'autres poissons d'eau vive et d'eau salée.

On a suggéré que le nom de la maladie de "tuberculose du poisson" soit changé en "mycobactériose" du poisson, à cause du manque de caractèristiques de base pour comparer la pathologie et les germes de la maladie. Ce nom concorde avec l'identification du germe chez différents poissons.

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(Figures 1–18 on following pages)

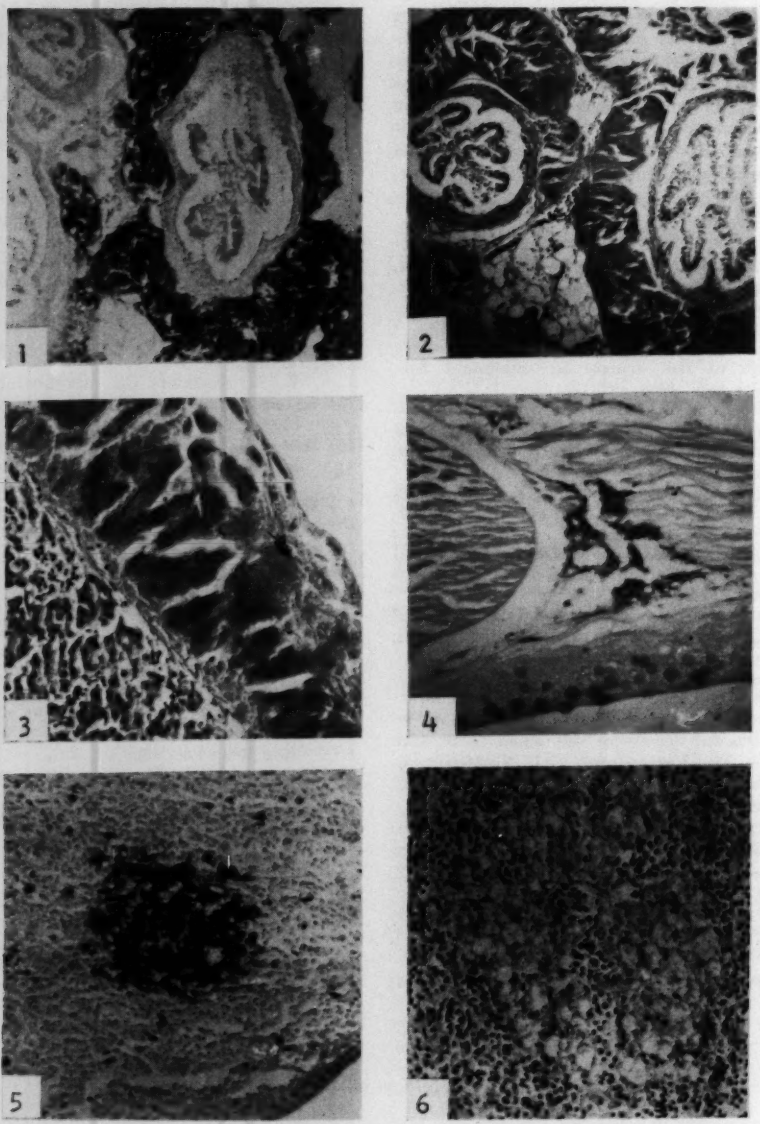


FIG. 1. A cross section through juvenile gastric ceca showing the great concentrations of organisms which surround the intestinal tract. The degenerate cecal mucosa is due to poor fixation (Fite-Faraco stain, × 80). FIG. 2. The same as figure 1, stained with hematoxylin and eosin stain, × 80. FIG. 3. Unaffected juvenile liver tissue surrounded by a typical peripheral zone of massed bacteria. The apparent cellular response in the liver tissue is due to normal nucleated erythrocytes. Only a thin band of fibrin encloses the bacterial mass (Hematoxylin and eosin stain, × 200). FIG. 4. A focus of infection in the ventral juvenile muscle wall. The surface epithelium is below (Fite-Faraco stain, × 100). FIG. 5. A typical circular lesion of proliferating organisms in the adult spleen (Fite-Faraco stain, × 200). FIG. 6. The same lesion as seen in figure 5 stained with hematoxylin and eosin, showing the epithelioid character of the cells (× 200).

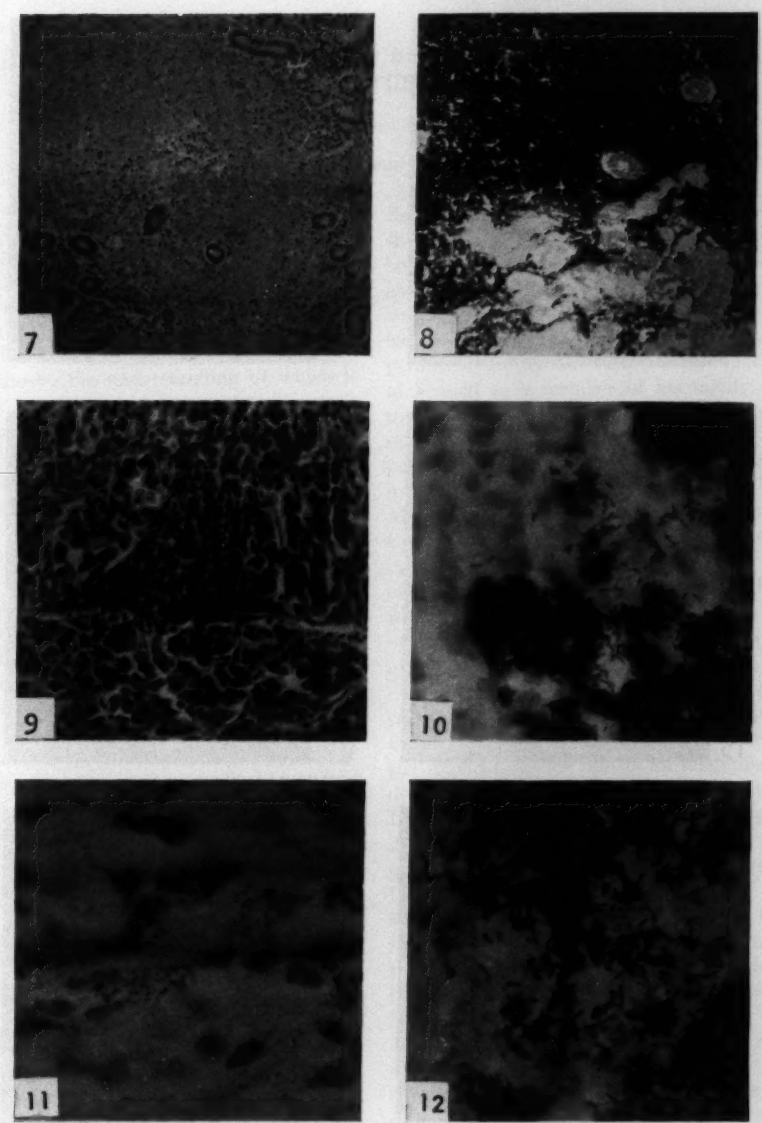
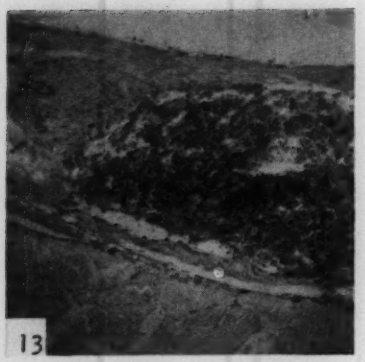
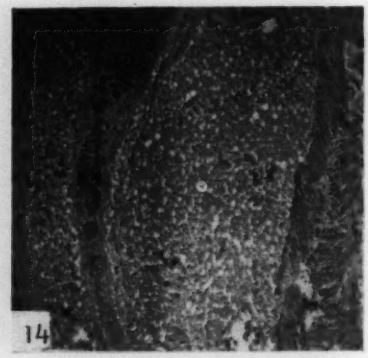
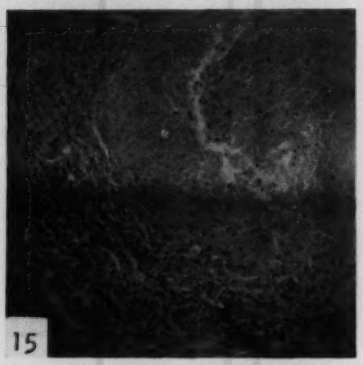
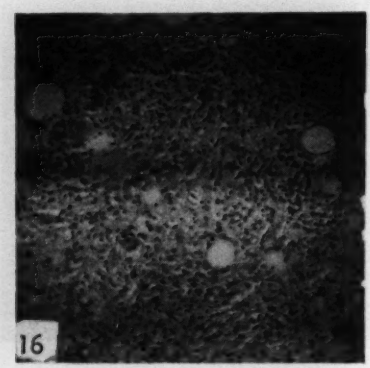


FIG. 7. A massive caseous lesion in the adult kidney. The apparent peripheral cellular response is normal hematopoietic tissue of the kidney (Hematoxylin and eosin stain, × 100). FIG. 8. The same type of lesion as figure 7 stained with the Fite-Faraco method (× 100). FIG. 9. The triangular area in the center consists of bacilli proliferating in adult liver parenchymal cells (Hematoxylin and eosin stain, × 200). FIG. 10. The acid-fast organism in section from the juvenile fish disease (Fite-Faraco stain, × 900). FIG. 11. The acid-fast organism in section from leprosy (Fite-Faraco stain, × 900). FIG. 12. The acid-fast organism in section from human pulmonary tuberculosis (Fite-Faraco stain, × 900).









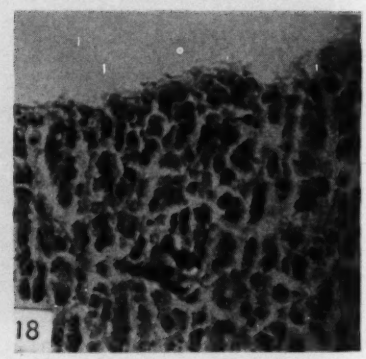


FIG. 13. The circumscribed lesion in the adult abdominal muscle wall (Hematoxylin and esoin stain, × 100). FIG. 14. The large areas of peri-intestinal caseous necrosis in the adult. The central strip is pancreatic acinar tissue. A portion of intestinal wall is seen on the far right (Hematoxylin and eosin stain, × 100). FIG. 15. A typical caseous tubercle from human pulmonary tuberculosis. (Hematoxylin and eosin stain, × 100). FIG. 16. The typical diffuse inflammatory reaction seen in leprosy (Hematoxylin and eosin stain, × 100). FIG. 17. Acid-fast bacilli seen in a section of adult chinook salmon tissue when stained by the Fite-Faraco method. Note the great numbers of organisms detectable by this method of staining. FIG. 18. The same section as in figure 17. Note the lack of detectable organisms when the section is stained by the Ziehl-Neelsen method.

THE INFLUENCE OF SOCIAL AND EMOTIONAL FACTORS IN THE TREATMENT OF TUBERCULOSIS[1, 2]

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Introduction

This paper is written from the experiences of a social worker in a rather *avant garde* Veterans Administration tuberculosis hospital on the edge of a large and complex city. These experiences have produced an orientation to the treatment of tuberculosis, the understanding of which is important for the consideration of the writer's observations. First, by "treatment of tuberculosis" is meant treatment which has its beginning in the hospital with continuation into the community once maximal hospital benefits have been achieved. Second, it is assumed that in the treatment of tuberculosis there are certain goals, some of which extend beyond the physical manifestations of the disease into some satisfying and socially productive life situation for the patient. Third, the key relationship in treatment is that existing between the patient and his physician, and no amount of additional services can substitute for the best possible medical care compassionately given. Last, questions will be raised in some of the areas of medical treatment and public health concepts which the writer lacks the competence to answer.

Observations

The Modern Milieu

The advances which have been made in the treatment of tuberculosis in the past ten years are truly miraculous and attest to the need to continue to encourage, nurture, and support both the spirit of inquiry and the dissatisfactions with things as they are. The means by which many of the social and emotional pressures in the treatment of tuberculosis can be minimized may be regarded as a by-product—really the end-product—of these scientific advances. It is known that tuberculosis hospitals do not have to be situated miles from nowhere, but that they can be easily accessible to adequate transportation and to the influences of the nonhospitalized community. This change of attitude decreased feelings of stigma, isolation, and separation and permitted the patient's continuing identification of himself as a member of his family and his society. Early sputum "conversion" through the skillful use of drugs makes it possible for the patient to visit his home frequently, to participate in family joys, sorrows, and problem solving. Much normal tension and anxiety, dammed up through curtailment of activity until it explodes in some "acting-out" way, can now be drained off through participation in more healthy life routines and in hospital activities, as the concept of enforced bed rest has been discarded for the majority of the patient group.

This same relaxation of enforced dependency enables a more comfortable emotional adjustment for the patient who was formerly threatened by the implications for him of surrendering to the demands of the dependent role. Fears about the future can also be minimized as knowledge of the disease and the effects of drugs and surgery permit the continuing reduction of inhospital time, promote prediction of length of hospital stay soon after admission, and eliminate the need for vocational changes which once characterized the impact of tuberculosis upon the life of the individual. The public health hazards represented by the alcoholic, unsocial, vagrant, and/or "Skid-Row" patient can be reduced by selective early surgery. Most important, these changes have made it possible to attract young, competent, curious physicians to the tuberculosis field, promising continuous progress in the treatment, and promoting treatment in an atmosphere of hope.

However, each advance creates its own set of new problems, and tuberculosis therapy is no exception: (*1*) There is the problem of the patient for whom tuberculosis was a way of life which is now being taken from him, with all of the

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anxieties inherent in any change in or dissolution of structure in which an individual has established some satisfying equilibrium. (*2*) Patients are being discharged to the community who have residual cavitary disease with noninfectious sputum which can become infectious again if the appropriate community supports are not there to maintain disease stability. (*3*) Among older patients, tuberculosis is only one of a number of diseases the patient may have and, without available medical care for this "total" person, his tuberculosis or general physical condition may again warrant hospitalization. (*4*) There are an increasing number of pulmonary cripples who are able to live outside the hospital provided they can have the various medications which aid breathing but which are extremely expensive. (*5*) The advances in medical treatment have also promoted the change from the concept of the tuberculosis sanatorium to that of the tuberculosis hospital with all of the characteristics of the hospital in terms of the pace of treatment and the necessity for distinction between need for active hospital care as opposed to maintenance medical care. Such a concept of the tuberculosis treatment institution emphasizes the plight of the hard-core infectious patient and the old "burned-out" tuberculous patient, both of whom may be best suited by all criteria for a sanatorium type of living. These advances imply continuous re-examination of the ways hospital and community resources can be modified to support medical progress and make it socially effective.

Patient and Therapist

The patient whose disease is being treated cannot be expected to have this perspective of tuberculosis treatment as outlined above. The experience has for him its own set of meanings and feelings. The understanding of these meanings and feelings, with a plan for maximizing the forces they represent in promoting the various phases of treatment and in minimizing the destructive forces inherent, are the challenge for his particular therapeutic environment. There are various ways in which this understanding may be acquired: assessment of intelligence, personality evaluation, social history, public health report of home environment, and a combination of all of these methods. However, what is really important is to know how the individual involved will function in the role of patient. To a social worker, emphasizing the understanding of the patient in relation to his total environment and the way he handles the day-by-day problems confronting him, it has seemed that understanding the social roles a person had been filling at the time he became ill and the way in which he was filling them would give some clue as to how he might function in the patient role and create awareness of his problems in assuming this role. Therefore, social role and social role performance are emphasized in this study.

Hospitalization or clinic attendance are both social situations and, consequently, the role of patient is a social role. As a social situation, hospitalization implies interaction among certain kinds of persons and interdependence of particular persons. Therefore, it is necessary also to consider the social role performance of the therapist and the interaction and interdependence of patient and therapist within a specific social structure. By "therapist" is meant any one of a number of persons with professional knowledge and skills who may be contributing to the treatment of the patient. By "social role" is meant the various roles in which life situations place people and the ways in which they are identified by others, i.e., mother, father, son, worker, neighbor, friend, et cetera. By "social role performance" is meant a "pattern of behavior (in fulfilling a specific role) which is expected by the society and is developed by the individual in response to social expectations qualified by his own individual expectations" (1).

In the qualitative assessment of an individual's role-performance, consideration may be given to the implications of the patient's chronologic age, his intelligence, his personality structure, as well as to the characteristics of the culture and the social milieu which he represents. Intrinsic in qualifying social role performance, the outer aspect of personal adjustment, is the understanding of the inner needs and adjustment of the individual. By this "inner adjustment" is meant "the way in which an individual achieves an integrated satisfaction of his various psychological needs which promotes a pleasurable sense of well-being and relative freedom from unpleasant tension and anxiety and which is maintained by the ability to deal with frustrating and threatening situations as they arise in a constructive fashion and with a minimum of handicapping stress" (2). It is also assumed that social

role performance is directed toward some goal which is desired by the person concerned.

For the greater number of patients, the social role and goals of a tuberculous patient have in no way been anticipated and come as a stark and shocking threat to his total way of life.

Mr. A., an American Indian from a southern tribe, migrated to the city several years ago in the hope of being able to provide more adequately for his wife and children. After considerable struggle with urban industrial organization, he had finally gained some security in union membership and a laboring job with a reputable corporation. It was at this point he had an hemoptysis, tuberculosis was diagnosed, and emergency hospitalization was effected. It could be expected that, as a husband, father, wage earner, in-migrant, and member of a minority group, his various identifications (dependent upon how he had adjusted to them) would influence the social and emotional stresses created for him by his hospitalization.

Mr. A. was initially extremely concerned about the health and welfare of his wife and children, saying repeatedly "if I could just know everything is going to be all right for my family I could settle down." The intervention of appropriate community resources was needed to assure their well-being. He was fearful of this mysterious threat to his life and made intensive use of hospital religious resources. Mr. A. ruminated on the meaning of his illness for him as a working man, as he was illiterate, had no vocational skills, and had to rely on his physical strength and willingness in work situations. These concerns were especially forceful when he had to make the decision for surgery. As a member of a minority group who had been subjected to additional discriminatory experiences once off the reservation, he was extremely sensitive to the way in which others related to him, and over-reacted to minor or imagined acts of discrimination. As an in-migrant the forces of his culture were still most prevalent, and he had a cultural concept of illness which had to be considered in helping him understand his tuberculosis. Also, as in-migrants, the family had lived precariously in slum conditions, and the health of the children was greatly threatened by the meager resources available.

As understanding of Mr. A. in relation to his culture and the purposefulness with which he had approached the complexities of migration increased, it was possible to see him as a man with great personal dignity and native intelligence, a good husband and father who took pride in carrying these roles responsibly. This understanding was a facilitating factor in his own comprehension of his illness and its treatment demands as well as in the direction of total therapeutic skills. The patient in turn was able to see the hospital more realistically as supporting him in obtaining the goals of his various social roles while concentrating on helping him become a patient.

For the therapist the situation is vastly different. One of his major social goals has been preparing through education and other conditioning processes to fill a role within a therapeutic setting. However, he is subject to as many judgments and pressures from within and without in fulfilling his therapeutic role as is his patient. Because each therapist also has additional social roles, he is as dependent upon the therapeutic environment as the patient is for assistance in clarifying the responsibilities and prerogatives of his role of therapist as differentiated from the responsibilities and privileges of his other social roles. He is much more consciously aware of his drive to succeed in the social role of therapist than the patient is to be a "successful patient" unless this is openly reduced to the simple terms of "the successful patient is the one who gets well." The therapist's success will depend to some degree on his understanding of his own professional self, his realistic expectations of his profession, his awareness of his own irrationalities and biases, and his willingness to recognize the limitations of his profession's competence and to seek the help of others.

Problems Created by the Treatment Setting

At some point in the continuum of their lives, the patient and the therapist come together within the treatment setting with one common purpose, but each with other recognized and unrecognized motivations which may be conflicting. As individuals and as groups they are dependent upon each other, and in dependency the basis for hostility toward the one depended upon is inherent. The patient for the most part depends upon the therapist to restore him to his "real life," and the therapist depends upon the patient to re-enforce his confidence in his profession and in himself as an effective therapist, and to provide the satisfaction in productive work, commendably accomplished, which is a part of healthy life adjustment. Consequently, not only the forces of his pre-hospital life create problems in social and emotional adjustment for the patient, but the whole hospital environment has the potential for creating its own set of stresses for him.

In conference with her supervisor a social worker brought up the fact that Dr. Y. was very

much upset by a new patient who had been admitted to his ward. He was sure the man was a homosexual as he shaved the hair on his chest, curled his hair, and talked in an effeminate way. Dr. Y. had expressed anger toward the patient and said he wasn't going to have him behaving that way on his ward. He was also sincerely concerned about how to "protect" his other patients from this man. As this had been brought up in conference with the worker, she inferred that Dr. Y. was asking her opinion and help, since they worked together closely and respected each other. Supervisor and worker thought that, unless the ward personnel could accept this patient as he was and understand him, the ward *would* have a problem on its hands and the patient would probably be forced to leave prematurely. Fortunately, the public health nurse had provided a home situation report at the time of the patient's admission which indicated he was a rather seclusive person, living with a male friend in an isolated rural home in what seemed to be a very compatible arrangement which created no problems for him or his community. Both men met the requirements of their jobs satisfactorily and seemed satisfied and comfortable in their life adjustment. It was suggested that, so long as his illness and hospitalization did not break up his relationship with his friend, it should be a supportive and stabilizing factor for the patient. It was further suggested that the patient be allowed to remain in a single room rather than be forced to accept a roommate and that staff pay no attention to his grooming so long as it did not offend hospital regulations or hygienic standards. The worker was encouraged to emphasize her acceptance of the patient and his behavior to help reduce other staff's anxiety and to encourage their sense of professional responsibility toward this man as a *patient* to whom other patients could give a bad time if they thought the staff wasn't accepting him. The patient remains hospitalized and seems to have made a place for himself within the ward group without creating any ward problems.

There are instances in which interest in and concern for the patient motivate staff demands for active participation in medical treatment or for using other therapeutic resources within the setting which are beyond the patient's capacities. Recognition of a patient's social roles and the strengths and weaknesses inherent in role performance may at times enable us to withhold as well as to proffer services or to modify the way services are given in order to accomplish therapeutic goals.

Mr. B., a 66-year old Negro native of Alabama, represents the group Dr. Frazier refers to as the "lower-class church-centered family which maintains some integrity of structure despite all the disorganizing influences around it" (3). The patient had worked hard at farming all his life, raised his children, and seen them migrate north to less precarious and more socially desirable life adjustments. He had overcome the handicap of the accidental loss of a leg in later years, and this had not deterred him in his work or in his support of his family. In his old age his children had prevailed upon him and his wife to rejoin them. He saw himself as a patriarch, a strong man able to overcome most handicaps, and a person in complete control of his life.

At the time his tuberculosis was diagnosed it was far advanced and, after six months of treatment, his sputum was still positive for tubercle bacilli, and drug changes were recommended which his physician attempted to discuss with him to obtain his agreement. Mr. B. indicated he didn't understand why they hadn't given him the right medicine in the first place and guessed he'd go home. Referral was made to the social worker to see what she might uncover to explain his attitude, the referring physician stating that the patient was "awfully dumb" and just didn't understand his disease.

A review of all of his records and an interview with the patient produced the foregoing information about the patient's social roles, his life, and his image of himself. From this material the social worker drew three inferences: Mr. B. was very much threatened by his illness which he could not understand and saw himself as losing control of his life to it and to the hospital; Mr B. could not express any decision which would indicate to others or to himself the relinquishment of control of his life and, if forced to do so, would leave the hospital; Mr. B. did not have the capacity or the orientation to illness to enable him to understand his disease intellectually. Efforts to help him understand were threatening, as they heightened his sense of being at the mercy of some mysterious power. It was suggested to the ward physician that the social worker withdraw and that he handle things matter-of-factly with the patient, not asking him to commit himself directly to any period of hospitalization but acting on the assumption that Mr. B. would cooperate if he was not required to express any overt capitulation to the hospital and to his illness. Mr. B. continues in the hospital and is accepting the changed medications. When seen by the social worker on a ward visit, he volunteered that he wasn't planning to leave until his new leg fit better—the nurse reports it fits beautifully. However, this is the way in which Mr. B. can make a comfortable inner and outer adjustment to the social and emotional demands of his illness and its treatment.

The patient who represents unsocial behavior patterns can be readily identified through the use of the social role and performance concept, and therapists can be alerted to the attitudes of helplessness, hopelessness, and poor motivation

which he brings to the treatment situation. Such a patient can be especially troublesome to the staff, and this anxiety can be transmitted to him in a variety of rejecting attitudes which may impel him from the hospital or set off a subtle rebellion against all treatment endeavors. These patients can both frustrate and manipulate therapists, encouraging latent "wars" among staff members unless they face and accept as a group this understanding of the type of person they are dealing with, accept the fact that they can affect only a little part of his total problem—his tuberculosis—and are willing to make the milieu and personal adjustments which will make this possible. At the Baltimore Veterans Administration Hospital, a preliminary rehabilitation review is conducted weekly, at which all professional services are usually represented, any one of which can select a patient for discussion. Some results of this review have been: group delineation and acceptance of some limited and essentially medical goal for severely disturbed or extremely sociopathic patients; productive and effective use of services to achieve these limited goals; clarity and comfort with therapists' expectations of each other.

Problems Created by the Patients' Community

In assuming the patient role, not only must the patient achieve some satisfactory adjustment between himself and the hospital environment; he must also establish some healthy equilibrium between himself as a patient and the world outside. To do this it may be necessary for him to relinquish, handle through others, or cope in a different way with his non-hospital social responsibilities. This can create its own set of emotional and social pressures for him. Family and personal resources may be inadequate, necessitating the patient's turning to established community resources for the desired assistance. Community agency resources may also prove inadequate to a particular patient's needs, may be surrounded by red tape, or devoid of any recognized identification with the interdependence and mutuality of health and welfare agencies in achieving both human and community goals. However, individual professionals are intensely aware of the part physical and emotional breakdown plays in creating social problems and of the needs for social supports to nurture the physical and mental health of an individual. Neither additional funds nor personnel will be readily available to achieve this "togetherness"; consequently, it becomes imperative that the manner in which efforts interact be continually re-examined so that there is maximal effectiveness in accomplishing human and social welfare goals.

Mr. C., a 69-year old Negro janitor, was referred for hospitalization with a notation from the clinic social worker that he had to arrange for the support of his wife and for her medical care before he could enter. He had resources in terms of eligibility for various benefits, but these were not readily forthcoming. The patient finally decided to come into the hospital because he thought his Department of Public Welfare application was well under way and his wife was urging him to care for himself. The establishment of the eligibility for public assistance dragged on and, just when everthing seemed set, the worker from the Department of Public Welfare realized that Mrs. C. would have to be the applicant rather than Mr. C. since he was hospitalized. (The worker did make a home visit on his own time to get Mrs. C.'s application.) Next, the question of Mrs. C.'s employability was raised; she was 62, too feeble to get to the Department's office, and was under the care of a doctor. His word could not be taken, however. The doctor from the Department of Welfare had to say she was unemployable, and the worker did not know when this physician would be able to make a home visit.

About this time Mr. C. was apprised that his wife was seriouly ill, but the family doctor would not go to see her. A visit by the public health nurse confirmed Mrs. C.'s illness and the nurse's belief that she should be hospitalized. The family doctor expressed his reluctance to visit Mrs. C. to the hospital social worker, stating he saw the problem more as a social than a medical one. He finally agreed that any social planning could be done only in the light of appropriate medical direction and said he would visit Mrs C. if some member of the family would call and ask him to come. As a result of his visit, Mrs. C. was immediately hospitalized as a medical emergency. Another phone call was made to the worker from the Department of Public Welfare advising of Mrs. C.'s hospitalization and raising the question whether her lack of employability could be attested to by the hospital. This was not possible; the State Medical Care Program would underwrite the cost of Mrs. C.'s hospitalization, but the City Welfare doctor would still be the only one who could pass on her employability. The death of the patient's wife the next day resolved this particular impasse. Had it not been for the kindly assistance of the patient's former employer in keeping the home going during this time, Mr. C. would probably have felt it necessary to leave the hospital.

Some Aspects of the Meaning of the Illness

The understanding of the patient's social roles and the ways in which he has filled them can be a key to understanding the meaning of his illness to him and the purposes it may serve for him in facilitating a more comfortable social role adjustment. In tuberculosis hospitals and clinics there are many men who have performed poorly in most of their social roles and who contract tuberculosis at a time when their hopes for achieving any small success are almost gone. The struggle has already been great and the prospect of resuming this struggle, when they are a little older and with the residuals of a chronic disease, becomes almost unbearable. These are the patients who often seek to consolidate the role of "patient" through emphasis on disability, numerous physical complaints, and negation of all rehabilitative efforts. Staff in turn may respond by emphasizing the commonly held principle that tendencies toward dependency should be discouraged in the handicapped and they sometimes become frustrated and angry when the patient refuses to "cooperate."

Dr. Paul Chodoff of the George Washington University Medical School, as a result of some of his documented observations (4) of chronically ill patients, states "there is room for doubt as to whether discouragement of dependency tendencies in the handicapped is always an invariably useful practice." He conjectures that "in some cases efforts to combat dependency may produce more comfort in their attendants than in the crippled persons themselves." That there is social status in being disabled is attested to by numerous pieces of legislation and journalistic presentations. The achievement of the role of a disabled person with its potential for various kinds of gratification to all concerned with the out-of-hospital life of the patient can represent the resolution of other social and emotional problems created by ineffective social role fulfillment.

Mr. D. is living happily as a totally disabled person with his ambitious schoolteacher wife who could not tolerate the threat to her own self-image and strivings he represented as an unskilled day laborer and cab driver. Their marriage had previously been characterized by many separations and reconciliations, mutual threats, and accusations. Mrs. D. now gets a great deal of recognition from her colleagues for her care of her husband and, in turn, is able to give to him so that he no longer needs to "run home to mother" for acceptance and appreciation.

The "Sanatorium" Patient in the Tuberculosis Hospital

Earlier in this discussion it was noted that the tuberculosis treatment center now has more characteristics of a hospital than of a sanatorium due to treatment advances and knowledge which enable definite determination of maximal hospital benefit from that treatment. For some few patients it is not quite so clear-cut, however. While they no longer need a hospital, they still need institutional or community supports to maintain the status quo of their disease and personal adjustment in terms of established social role fulfillment. Consequently, this termination phase of active treatment can pose its own set of social and emotional pressures. After prolonged hospitalization and a stressful and complicated medical course, a patient may find he can at last achieve his goal of leaving the hospital but that he has no social role left to him other than that of institutionalized patient; his family, if any, has adjusted to his absence and established a new equilibrium, his community has changed, and it may have deprived him of his rights and privileges as a citizen through loss of residence status.

Mr. E. has been a patient in tuberculosis hospitals continuously since 1953, most of which time was spent in the state hospitals. Although young, he has extensive disease, has had radical surgery, and each breath is a small victory. He has reached the point where he could live outside the hospital if a suitable social situation could be established. He is not considered employable, and his community has no sheltered work program which he could fit into. Although he is eligible for Veterans Administration hospitalization at the rate of about $20 per day, as he was not in the service long enough, he is ineligible for a Veterans Administration pension of $66 monthly which would facilitate his discharge. He was eligible for hospitalization by the state for five years, but is considered a nonresident for public assistance purposes because he spent a year in California and had only been back in his native city for ten months before he had to re-enter the hospital in 1953. Mr. E. brings a weltering of social and emotional conflicts to his various therapists each day; they are equally confused by the contradictory roles in which his community sees him.

The hard-core patients with sputum positive for tubercle bacilli are particularly prone to

"role" and "goal" confusion when it has been determined that nothing other than isolation can be accomplished by continued hospitalization. The hospital therapeutic team sees its goals as those of delineating the nature of the patient's disease, doing what can be done about it, declaring an end-point to the results to be obtained from active medical care, and then making it possible for the patient to live in an accepting community in a supportive and satisfying social situation. At the same time, public health counterparts—equally as conscientious and with equal professional integrity—see their roles and goals as those of isolating the patient and protecting the community from him. These differences are healthy and for the most part will be reconciled to the advantage of both patient and community. However, unreconciled, they can create extensive turmoil for both patients and therapists.

It is recognized, too, that hospitals contain a small group of patients who have neither the social nor personal resources to assume any social role other than that of institutionalized patient if the benefit achieved from prolonged and expert medical and social care is to be sustained. Hospital staffs have the choice between accepting the fact that a few persons must remain hospital patients so long as they live (or until a more appropriate community resource appears) and making life as satisfying as possible within this context, or compromising for an inadequate social situation which sooner or later will result in the patient's being readmitted in an extremely demanding state of physical debilitation. It is not difficult to imagine the panic created in the old, sick person who has experienced the progressive loss of his physical and social resources, whose world outside the hospital has all but disappeared, whose vigor for coping with the complexities of an unsheltered living situation has deserted him, and who feels alone and lonely, deserted, depressed, and frightened when he is told he can make a plan for himself outside the hospital. When, already in panic, he is faced with staff attitudes which fail to accept his extreme dependency, his loss of capacity for community living, and his inability to muster meager or nonexistent social and personal resources, his hopelessness and helplessness can create their own set of additional problems for staff. Overt and subtle role and goal clashes can occur as the ward presses for discharge while the patient, the community, and the hospital social worker may all be in agreement that, community resources being what they are, the patient is right where he should be—in the hospital.

Discussion

This study began with the highlighting of the social and emotional implications of tuberculosis treatment in its present phase. Then, while recognizing that the social and emotional factors influencing the treatment of tuberculosis can be identified in a variety of ways and treatment planned accordingly, the concept of social roles and role performance was emphasized to assist in understanding patients, therapists, and what happens when they come together in the treatment setting, as well as the social and emotional problems this "coming together" can create. The belief has been expressed that, although the patient cannot usually be changed, it is frequently possible for staff through understanding and examination to change the ways in which therapeutic roles are performed. The staff can also effect changes in the treatment setting which will enable the patient to use therapists and settings to the fullest extent of his capacities for treatment participation. Throughout this discussion, case illustrations have emphasized the writer's identification as a social worker with the individualization of the patient as the primary approach to understanding the meaning and implications of the illness and treatment experience for him. Finally, it has been implied that, with the shift to the tuberculosis hospital in contrast to the sanatorium, knowledge of the epidemiology of the disease, and the trend toward carrying on much of the sustaining treatment in the community, therapists must involve themselves in a process of continuous evaluation and rethinking of the roles of community agencies as they influence and are influenced by the social and emotional problems of the tuberculous patient.

As a means of consolidating some of the foregoing material, one more case illustration is offered which vividly illustrates the use of the social role concept in facilitating treatment:

Mr. F. is a short, slight, old Negro gentleman, who had a variety of illnesses when he came to the hospital and who created minor nursing crises by the personality disorganization which he manifested. There were various brief contacts with social work service regarding his retirement

papers, arranging to handle some business matters through a family member, and minor family misunderstandings which arose. During these contacts the social worker began to see Mr. F. not as a sick, disorganized old man with few assets other than his gentle nature and gentlemanly deportment. He was revealed as a respected, competent employee of thirty years service with the Custodial Service in the Senate Office Building. He was a real patriarch who was purchasing the family home and who had provided responsibly for his family and kept its members together and loyal to each other in a community of many divergent social forces; he was a good brother whose sisters respected him and helped him; and he was a lodge member and churchman. The separation from all of these social supports into the unfamiliarities of his first hospitalization had hastened and emphasized personality disorganization, which might not have been so noticeable, or important in his adjustment, in his accustomed social setting.

Eventually Mr. F. achieved maximum hospital benefit status, and his concerned and capable physician despaired as to what would happen to him upon discharge. The social worker had to support the physician through the strength of her conviction that a very adequate discharge plan could be constructed out of the social strengths which Mr. F. represented, regardless of the way he presented himself to hospital personnel. Mr. F. was discharged to an excellent home-care plan, and evaluation a month later by the Veterans Administration Regional Office Social Work Service indicated that the patient and family were managing very well.

Through an administrative error, Mr. F. was called back to the hospital several months after discharge for a recheck of his tuberculosis. His family brought him to the hospital, but the recheck ward staff, not being familiar with the patient's situation, had made no plan with them for his return home. The social worker was asked to make a plan as it was not thought Mr. F. could deal with the complexities of railroad or bus stations on a summer Friday afternoon. Mr. F. agreed he would like some help, but discouraged calling his daughter who gave him the major part of his care, as he thought she should enjoy the freedom which this brief hospitalization had permitted her. Then this little, old, sick, disorganized man said, "I'll tell you what to do. You just call the Capitol, and you ask for the Senate Office Building, and then you ask for Mr. J. and he'll have my brother-in-law come get me." So the social worker called the Capitol of the United States.

Summary

Modern treatment methods for tuberculosis serve to minimize some of the social and emotional problems of patients. However, these same advances have created new problems for patients, hospitals, and communities. Especially noteworthy are the plight of the "sanatorium" patient in the tuberculosis hospital of today and the panic of the patient who had found, through illness, a socially acceptable way of life.

Patients fill many social roles, such as husband, father, worker, et cetera, before assuming patient roles. Some understanding of these roles and assessment of performance in them and the threat to that performance inherent in illness and hospitalization can enable realistic treatment plans and promote the social role of "patient."

Clarity of therapists in assuming therapeutic roles as differentiated from other social identifications can do much to avoid situations in which patients manipulate staff by neurotic or deviant behavior or by behavior which can provoke staff responses based on nonprofessional social roles. Such clarity can also facilitate coordination of therapeutic services, minimizing staff differences which some patients can encourage and which can prevent accomplishment of optimal treatment plans.

The relationships of patients with treatment settings or community services can frequently present as many obstacles to successful performance of patient roles as can other social identifications. Some modification of these pressures can nurture capacities for adaptation and is frequently more possible than basic changes in patients' personalities or in the extra-hospital milieu.

Sumario

El Influjo de los Factores Sociales y Afectivos en el Tratamiento de la Tuberculosis

Los modernos métodos terapéuticos para la tuberculosis sirven para amenguar algunos de los problemas sociales y afectivos que asedian a los enfermos. Sin embargo, esos mismos adelantos han creado nuevos problemas para los enfermos, los hospitales y las colectividades. Dignos de nota en particular son el aprieto del enfermo "sanatorial" instalado en el actual hospital para tuberculosos y el pánico del sujeto que había encontrado, gracias a su enfermedad, una forma de vida socialmente aceptable.

Los enfermos ocupan puestos sociales, como son los de esposo, padre, operario, etc., antes de tomar el de enfermo. Alguna comprensión de esos puestos y valoración del desempeño de los mismos y del peligro creado a ese desempeño que va inherente con la enfermedad y la hospitalización puede facilitar la formulación de planes realistas de

tratamiento y fomentar el papel social del "enfermo."

La agudeza del terapeuta en la apropiación de los papeles terapéuticos, diferenciados estos de otras connotaciones sociales, pueden servir de mucho para evitar situaciones en las que los enfermos manipulan el personal técnico con su comportamiento neurótico o caprichoso o por comportamiento susceptible de provocar reacciones de parte del personal, basadas en papeles sociales que no son profesionales. Esa agudeza también puede facilitar la coordinación de los servicios terapéuticos, reduciendo al mínimo las diferencias de ideas en el personal que algunos enfermos tal vez alienten y que pueden impedir la ejecución de los planes óptimos de tratamiento.

Las relaciones de los enfermos con la escena del tratamiento o los servicios colectivos pueden frecuentemente aportar tantos obstáculos al éxito del enfermo en el desempeño de sus papeles como otras identificaciones sociales. Alguna modificación de estas presiones puede reforzar las capacidades para la adaptación y a menudo resulta más factible que introducir alteraciones fundamentales en la personalidad de los enfermos o en el medio extrahospitalario.

Resume

L'influence des facteurs soçiaux et émotionnel dans le traitement de la tuberculose

Les méthodes modernes de traitement de la tuberculose servent à diminuer l'importance des problèmes sociaux et émotionnels des malades. Cependant, ces mêmes progrès ont crée de nouveaux problèmes pour les malades, pour les hôpitaux et les communautés. Il faut noter spécialement la condition du malade de "sanatorium" dans l'hôpital de tuberculeux d'aujourd'hui et la peur du malade qui a trouvé, à travers la maladie, un moyen de vie acceptable.

Les malades remplissent de nombreux rôles soçiaux, tels que mari, père, travailleur etc. . . ., avant d'assumer celui de malade. La compréhension de ces rôles et l'évaluation de cet accomplissement chez eux, et la crainte de cet accomplissement inhérente à la maladie et à l'hospitalisation, peut permettre des plans réalistes de traitement et faciliter le rôle social de "malade."

Une explication claire des thérapeutes des rôles thérapeutiques présumés les différençiant des autres entités sociales, peut faire beaucoup pour éviter des situations ou les malades manoeuvrent le personnel par un comportement neurotique ou non adapté, pouvant provoquer de la part du personnel des réponses basées sur des rôles sociaux non professionnels. Une telle explication peut aussi faciliter la coordination des services thérapeutiques, diminuant chez le personnel les différents que quelques malades peuvent encourager et lesquels différents peuvent nuir à l'accomplissement optima des plans de traitement.

Les relations des malades avec le milieu ou ils sont traités ou les services de communauté peuvent présenter fréquemment autant d'obstacles à un succès dans l'accomplissement du rôle de malade, que dans d'autres identités sociales. Une modification quelconque de ces tensions peut fournir des possibilités d'adaptation et est souvent plus possible que des changements radicaux de la personnalité des malades ou du milieu extrahospitalier.

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Case Reports

UNUSUAL CLINICAL AND ROENTGENOGRAPHIC FEATURES OF PULMONARY INFARCTION[1]

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Introduction

Pulmonary embolism and infarction are conditions which, despite long recognition, are still more often missed than diagnosed. These serious conditions occur more frequently than was previously thought. The short duration of symptoms, the scant physical findings, and the transient and often minimal electrocardiographic findings are added obstacles to making the diagnosis. Unusual clinical findings add considerably to the difficulties of the problem. The object of this report is to present illustrations of unusual roentgenographic and clinical findings of pulmonary infarctions. The following case presentations are illustrative of pulmonary infarctions which resulted in diagnostic errors on the part of the attending physicians.

Case Reports

Case 1. R. H., a 37-year-old Negro laborer, was admitted to the Kings County Hospital Center on February 6, 1952, because of a cough and low-grade fever for one month. He had expectorated about 30 ml. of fresh blood on the day of admission. The roentgenogram of the chest showed an exudative parenchymal infiltration in the posterior segment of the right upper lobe (figure 1). His temperature was 99.8°F. Two sputum specimens were positive for acid-fast bacilli on microscopy. Cultures of the sputum and gastric washings were negative for *Mycobacterium tuberculosis*. Streptomycin, 1 gm. twice weekly, and PAS, 12 gm. daily, were administered.

The course in the hospital was as follows: The pulmonary lesion failed to improve and, on May 4, 1952, 50 mg. of isoniazid four times daily, with 50 mg. of pyridoxine once a day, were added to his therapy. In June, 1952, because of the appearance of cavitation within the lesion even though the antituberculous therapy was considered adequate, pneumoperitoneum was added to the therapy. The serial chest roentgenographic studies showed continued increase in size and extension of the area into the apical segment of the lower lobe (figures 2, 3). On bronchoscopic examination, January 9, 1953, an injected, indurated, fixed and contracted right upper lobe bronchus was found. Cultures of the bronchial washings were negative for acid-fast bacilli, and on cytologic examination no tumor cells were found. Because of the history, symptoms, sputum positive for tubercle bacilli on microscopy, and the progressive clinical course, it was thought that the patient had tuberculosis with a coexistent pulmonary neoplasm (4).

On February 25, 1953, a resection of the apical and posterior segments of the right upper lobe was performed. The report of the pathologist was infarction of the lung, recent, and organizing. On microscopic examination, areas of recent infarction and areas showing thickened alveolar walls with large numbers of hemosiderin-laden macrophages within the alveoli were found. The arteries were sclerosed. In the bronchi a sanguinopurulent exudate was present. Fibrous pleuritis was also noted. No evidence of tuberculosis or neoplasm was found.

The postoperative course was uneventful and the patient was discharged to the outpatient department on May 22, 1953.

Case 2. A. G., a 34-year-old Negress, was admitted to the Kings County Hospital Center on March 26, 1958, with a two-day history of cough productive of brown sputum, pain in the right chest and shoulder, shortness of breath, and chills and fever. On examination, her temperature was 105°F.; her pulse rate, 110 per minute; respirations, 30 per minute. Dullness, diminished breath sounds, and moist rales were found over the right upper lobe. The laboratory studies were all normal except for the leukocyte count which was 2,300 per cu. mm. with a differential count of 21 per cent segmented forms, 78 per cent lymphocytes, and 1 per cent monocytes. Skin tests with histoplasmin and coccidioidin were negative, but a positive reaction was obtained to first-strength PPD. Culture of the sputum gave growth of colonies of coli-aerogenes bacilli. *M. tuberculosis* was not found on culture. A serologic test for syphilis (VDRL) and cold agglutinins were reported as negative.

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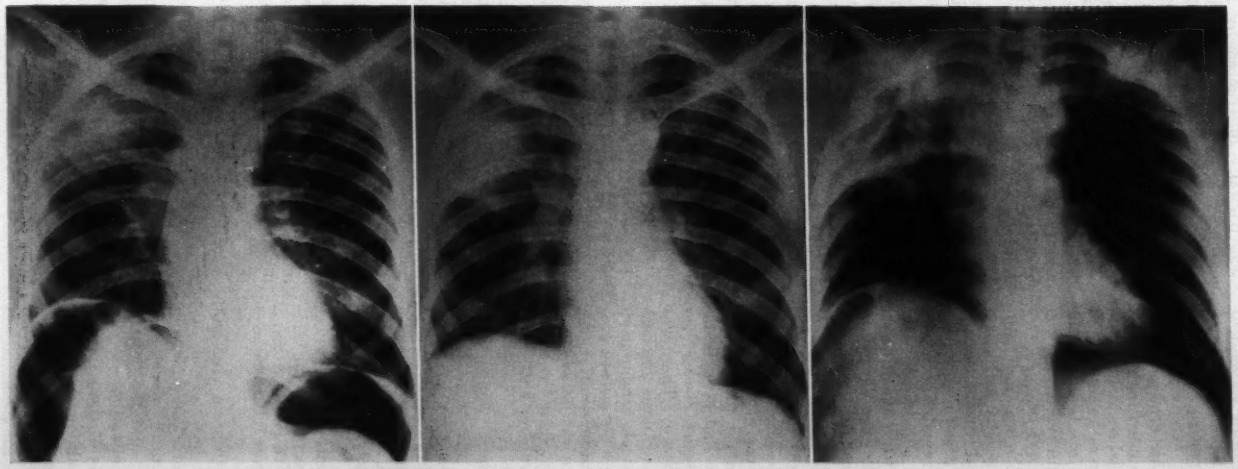


FIG. 1 (Left). Posterior chest film made on April 20, 1952, showing exudative infiltrate involving the posterior segment of the right upper lobe.
FIG. 2 (Center). Posterior-anterior film a month later showing exudative infiltrate involving the anterior and posterior segments of the right upper lobe. Pneumoperitoneum is present.
FIG. 3 (Right). Anteroposterior tomographic study. Multiple cavities may be noted.

The posterior-anterior teleroentgenographic study showed consolidation of the posterior segment of the right upper lobe. With the administration of penicillin, a lowering of the temperature occurred by lysis.

Further chest roentgenographic studies failed to show resolution of the consolidated segment. A round density of the anterior basal segment of the right lower lobe was noted later as an additional finding. Cavitation of the upper lobe lesion with a free-floating round density within the cavity was present at this time (figures 4–6).

The bronchoscopic examination was not helpful. An exploratory thoracotomy was performed on May 7, 1958, for diagnosis and treatment. The preoperative diagnosis was cyst with fungous ball, aspergillosis, or a bronchogenic cyst. The report from the pathologist described a pulmonary infarct with abscess formation, within which was a loose ball of necrotic lung tissue. The density in the lower lobe proved to be a bronchial cyst with attachment to the esophageal wall.

Case 3. J. W., a 71-year-old white male, was admitted to the Kings County Hospital Center on January 9, 1955, because of fever of 103°F. for three days and severe dyspnea for four weeks. For the previous five years, he had been under treatment for arteriosclerotic heart disease, requiring digitalis and diuretic therapy. There was no history of cough, hemoptysis, cyanosis, or chest pain. On admission the physical examination showed an acutely ill man with a temperature of 102°F., a pulse rate of 120 per minute; respirations, 30 per minute; the blood pressure was 160 systolic, 80 diastolic in mm. of mercury. The chest was barrell-shaped and fixed in inspiration. The breath sounds were diminished at the bases. Rales or rhonchi were not present. The heart sounds were distant, and a systolic murmur was heard in the mitral area. The abdomen was normal. Ankle edema was minimal. The following laboratory findings were recorded: blood urea nitrogen of 36 mg. per 100 ml., a leukocytosis of 38,500 per cu. mm., with an increase in the polymorphonuclear cells.

The roentgenographic examination of the chest was interpreted as showing a caseopneumonic infiltration of the left upper lobe with two cavities; a bronchogenic spread to both lower lobes was also noted.

Antituberculous therapy (streptomycin and PAS) was administered on the basis of the appearance of the roentgenogram. The following day, acute left ventricular failure developed. Response to therapy was poor, and the patient died on the sixth day of hospitalization.

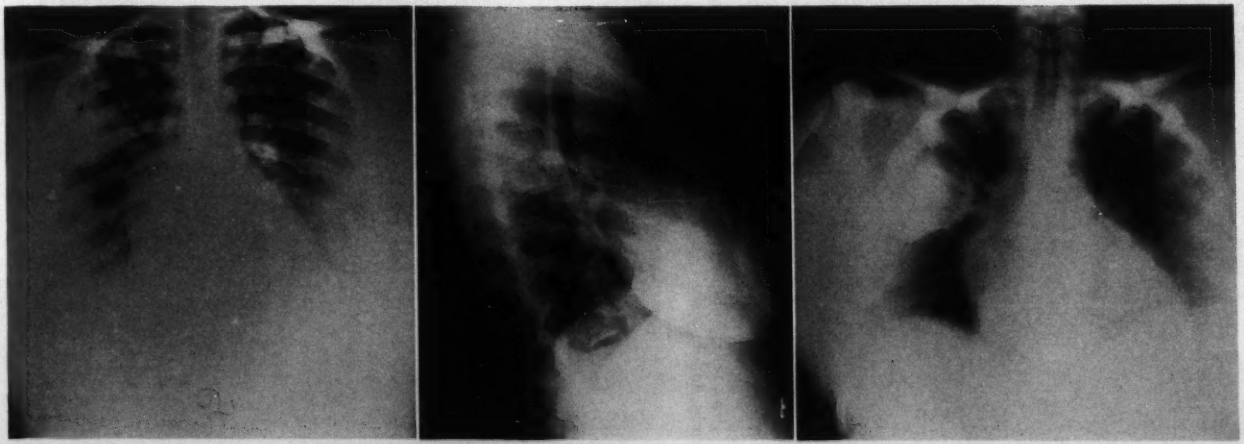
At autopsy, phlebothrombosis of the left femoral vein, multiple bilateral pulmonary emboli, bronchopneumonia with organizing multiple abscesses, and diffuse myocardial fibrosis and myocarditis were found. A chronic pleuritis was noted on the right. A large thrombus was adherent to the intimal surface of the right pulmonary artery. The lumen of the right pulmonary artery was partially obstructed by a thrombus which extended into the peripheral branches. Many of these branches were completely obstructed. Another thrombus was located in and partially obstructing the left pulmonary artery. At the apex of the left lung, a 5-cm. thin-walled cavity filled with grayish purulent material was found. Areas of pneumonic consolidation surrounded the cavity. No evidence of tuberculous inflammation was found even after special studies. The cavity resulted from necrosis of the area of pulmonary infarction.

Case 4. A. T., a 59-year-old white male, was readmitted to Kings County Hospital Center on March 28, 1956, because of marked shortness of breath of ten days' duration. The patient was known to have pulmonary tuberculosis and had had previous admissions in 1939 and 1955. He had lost 10 pounds in the two months prior to the present admission. Hemoptysis and chest pain were not noted. Abnormal physical findings were dullness over the left chest with absent breath sounds and increased vocal fremitus. A roentgenographic examination of the chest was unchanged from that made in 1955. An encysted fluid collection along the axillary portion of the left hemithorax was still present, but a well-defined nodular density of the superior segment of the right lower lobe was a newer finding (figures 7, 8). The sputum was negative for acid-fast bacilli on culture.

The patient's course rapidly worsened and he died on April 19, 1956. The clinical diagnosis was bronchogenic carcinoma of the right lower lobe. On post-mortem examination, pulmonary tuberculosis with complete destruction of the left lung, an adherent left pleura, and an infarcted middle lobe were found. The infarct was circumscribed, and measured 5 cm. in diameter. Cirrhosis of the liver, hemorrhages of the right adrenal, and secondary amyloidosis of kidneys and spleen were additional findings.

Case 5. A 69-year-old white male with a history of Parkinsonism for thirty years was admitted to the hospital in coma. Two weeks prior to admission, sudden severe shortness of breath, loud breathing, and pain on respiration occurred. Difficulty in swallowing was also present. For the ten days prior to admission he also had periodic lapses of consciousness. Six days prior to admission, he developed a nonproductive cough and chest pain. The following day he became incontinent of urine and feces. He was then placed in a nursing home. The day before admission, the patient was noted to be markedly jaundiced; one member of the family had noted a slight yellow discoloration on the patient's face six days previously. The patient was found to be unresponsive and was sent to the hospital.

Prior to the onset of the present illness, no history of chest pain, dyspnea, cough, hemoptysis, precordial pain or discomfort, palpitation, cyano-



FIGS. 4 and 5 (Left and center). Anteroposterior and lateral chest roentgenograms showing an infiltrate involving the posterior segment of the right upper lobe. Cavitation and pleural effusion were present.

FIG. 6 (Right). The anteroposterior tomogram which shows that the cavity contains a large dense mass within it, which seems free and floating within it. This strongly resembles a fungous ball usually seen in aspergillosis.

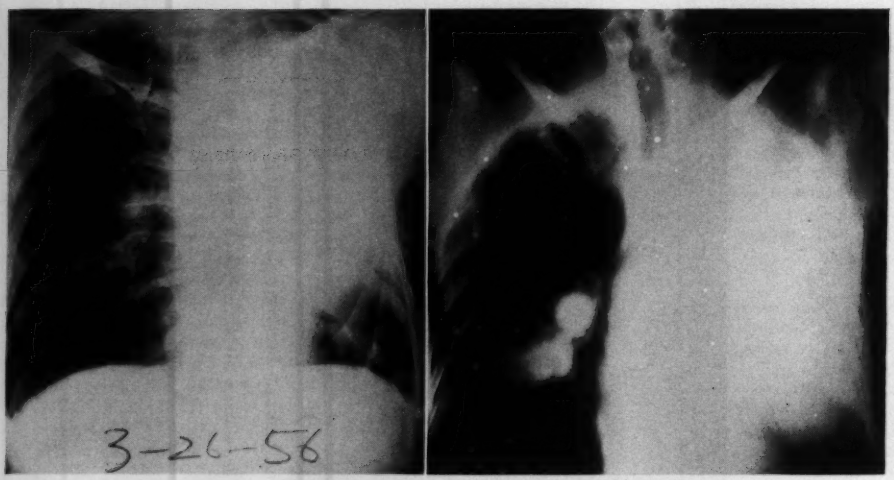


FIG. 7 (Left). Posterior-anterior chest film. Encysted fluid collection extending along the axillary position of the left hemithorax. A well-defined nodular density is present in the superior segment of the right lower lobe overlying the eighth posterior rib. This recent abnormal finding suggested a bronchogenic carcinoma.

FIG. 8 (Right). Anteroposterior chest tomogram. The well-defined density measuring about 3.5 cm. in diameter may be noted in the right middle lobe.

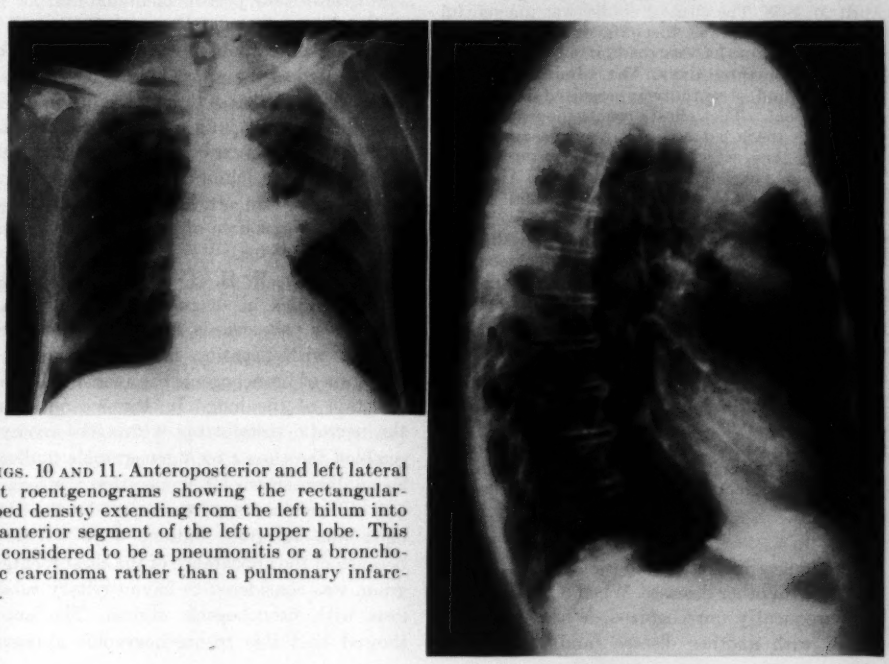
FIG. 9. Anteroposterior chest roentgenogram showing the extensive cavitary and necrotic disease of the left upper lobe and the rounded density just above the diaphragm on the right. This was thought by the attending physicians to represent tuberculosis or bronchogenic carcinoma rather than pulmonary infarction.

sis, or edema was elicited. The patient, however, had been sleeping on two pillows for an unknown period of time.

On physical examination on admission, a poorly nourished and debilitated, semicomatose, elderly man in a semirecumbent position was described. He was breathing rapidly with great effort. His temperature was 102°F.; pulse, 85 per minute; respiration, 36 per minute; blood pressure, 130 systolic, 80 diastolic in mm. of mercury. The skin was markedly icteric and of poor turgor. An ecchymosis was noted in the left flank. The left pupil showed evidence of a previous iridotomy, and the right pupil reacted poorly to light and accommodation. The sclerae were markedly icteric. The oral mucous membranes were dry. The neck veins were not distended. The anteroposterior diameter of the chest was increased and the respiratory excursions were diminished but equal. Dullness and poor breath sounds were found over the lower two-thirds of the left lung field. Rales were not heard. The cardiac border could not be outlined. The point of maximal impulse of the heart was neither visible nor palpable. The heart sounds were distant and the rhythm was irregular, with many ventricular extrasystoles. No murmurs were heard. The abdomen was soft and nontender; no organs or masses were palpable. There was minimal bilateral ankle edema. The dorsal pedal pulsation was felt. A dry, decubitus ulcer, 4 cm. in diameter, was found in the sacral region. On rectal examination thrombosed external hemorrhoids and diffuse enlargement of the prostate without nodules were noted. A cog-wheel type of rigidity of the extremities and the neck was present. Deep tendon reflexes were normal. The Babinski sign was absent.

The laboratory findings on admission were: hemoglobin, 15 gm.; hematocrit, 46 per cent; erythrocyte sedimentation rate, 35 per min. per hour. The leukocyte count was 18,300 per cu. mm. The differential count of the blood smear was polymorphonuclear cells, 95 per cent; lymphocytes, 5 per cent. The erythrocytes showed anisocytosis, poikilocytosis, and target cells; the platelets appeared adequate. The urine examination showed an amber-colored urine with slight cloudiness. The reaction was acid. Albumin was 1 per cent; the sugar was negative, and a positive test for bile was present. The urobilinogen was positive in 1:64 dilution. The microscopic examination showed an occasional leukocyte and 5 to 6 coarse granular casts per high-power field. Blood chemistries: blood urea nitrogen, 63 mg. per 100 ml.; sugar, 50 mg. per 100 ml.; cholesterol, 172 mg. per 100 ml.; chlorides, 114 mEq/L; creatine, 2.5 mg. per 100 ml. The prothrombin time was 22.8 seconds (control 12.8 seconds). Examination of the color of the stool was reported as brown, and occult blood was noted.

The admission chest roentgenogram revealed "pneumonic infiltration in the upper half of the left lung and a similar patch at the right lung base" (figure 9). On the day of admission a left



FIGS. 10 AND 11. Anteroposterior and left lateral chest roentgenograms showing the rectangular-shaped density extending from the left hilum into the anterior segment of the left upper lobe. This was considered to be a pneumonitis or a bronchogenic carcinoma rather than a pulmonary infarction.

thoracentesis was done and yielded about 50 cm. of serosanguineous fluid. This fluid contained 2,275 leukocytes per cu. mm., 80 per cent of which were lymphocytes and 20 per cent polymorphonuclear cells. No organisms were cultured from it. A lumbar puncture, done on the first hospital day, showed a clear yellow fluid with normal pressures, and the microscopic examination was normal. Tracheal suction on the fourth day in the hospital produced a rusty mucoid semiliquid material which contained gram-positive diplococci and numerous polymorphonuclear leukocytes. No acid-fast organisms or Klebsiella were seen on the smear.

The patient was placed in an oxygen tent and given an intravenous infusion of dextrose in water and potassium penicillin, 10 million units per day. In spite of this treatment, the patient remained semicomatose and continued to be jaundiced. A spiking fever to 104.4°F. was present throughout. Tachycardia and tachypnea remained. The blood pressure fell to 80 systolic, 50 diastolic in mm. of mercury on the fifth hospital day. Measures were used to maintain the blood pressure, but the patient died on the sixth hospital day.

Multiple pulmonary infarctions with necrotic abscesses were found on post-mortem examination. The source of the emboli was from mural thrombi of the right ventricle.

Case 6. A. J., a 65-year-old male, was admitted for the first time to Kings County Hospital Center on April 29, 1958. A cholecystectomy was done on April 20, 1958. The clinical course was uneventful and the patient was discharged. Because of a wound infection, he was readmitted with a fever of 103°F. for three days. The administration of penicillin and streptomycin resulted in clinical improvement. The chest roentgenographic examination disclosed an infiltrative lesion in the left upper lobe, which was thought to represent a bronchogenic carcinoma (figures 10, 11). All of the laboratory studies were within normal limits. The examination by bronchoscopy was essentially negative. Evidence of an old anterior wall myocardial infarction was noted on the electrocardiogram. A biopsy of the scalene node was done and, on examination, was reported as showing reticuloendothelial hyperplasia. A resection of the left upper lobe was performed on June 5, 1958. The pathologist reported that this lung specimen contained a pulmonary infarction. The microscopic diagnostic report was an abscess of an infarcted area of the anterior segment of the left upper lobe due to an organizing thrombus in the branch pulmonary artery. An extensive organizing pneumonitis was also noted.

Discussion

Pulmonary infarction occurs alone or in association with other diseases. When it occurs alone, it is frequently unrecognized. When it is associated with another disease (and especially a pulmonary disease), it is more difficult to diagnose; in fact, the consideration of pulmonary infarction is lessened. The clinical histories presented show how faulty the diagnostic considerations may be when abnormal densities are found on the chest roentgenograms, especially when associated with other abnormalities. An unorthodox appearance for pulmonary infarction on the roentgenogram has been described (1). A pulmonary infarction may and can masquerade as any pulmonary condition. The classical symptoms, pleuritic pain, cough, and hemoptysis, and the typical electrocardiographic changes are more often absent than present. The diagnosis of pulmonary infarction is often made only after surgery or by autopsy. The presence of cardiac disease, phlebitis, phlebothrombosis, or a history of recent surgery or severe trauma, strongly suggests a pulmonary infarction to explain abnormal roentgenograms. Pulmonary embolism may occur, however, without these predisposing factors. Cohen and Dale documented eight cases which presented without any appreciable causative factors (2). The presence of jaundice, especially in a patient with heart disease, should suggest pulmonary infarction.

A review of the post-mortem material for 1957 at the Kings County Hospital Center of 130 pulmonary infarctions revealed that 10 per cent were located in the upper lobe (3).

Davidson reported three cases and reviewed the literature of lung abscess resulting from aseptic pulmonary embolism. He called attention to the frequent clinical manifestation of pulmonary infarction as a lung abscess of the upper lobes (4). The source of the emboli in his cases were the leg veins.

The patient R. H. (*Case 1*) is an example of the difficulties in diagnosis. In this instance, pulmonary tuberculosis, and finally the rounded density with negative findings suggested the diagnosis of bronchogenic carcinoma. This led to resection of the lung. In the second patient, the necrotic tissue lying within the cavity resembled the classic roentgenographic finding for aspergillosis. Even after operation the diagnosis was still retained until the report by the pathologist was received. Patient J. W. (*Case 3*), because of the appearance of the chest roentgenogram, was considered to have cavitary tuberculosis with bronchogenic spread. The autopsy showed that this roentgenographic appearance

was due to necrosis of the infarcted area and multiple infarctions of both lower lobes. The fourth patient, A. T., was also suspected of a bronchogenic carcinoma in the middle lobe. Many of these unusual manifestations of pulmonary infarction, especially the nodular densities, are often erroneously diagnosed as bronchogenic carcinoma. If the clinical features and the history are weighed, the correct diagnosis can be established. It is important that the correct diagnosis be made so that proper therapy can be given.

Suspicion of pulmonary infarction should be entertained in patients with bronchogenic carcinoma. The incidence of pulmonary emboli is frequent in these patients. Several of the patients in this hospital with bronchogenic carcinomas developed pulmonary infarctions of the upper lobes.

Pulmonary disease in the upper lobes is not usually considered to be pulmonary infarction; but, when a necrotizing pneumonia, abscess formation, and rounded densities unexplained by the usual causes are present, then pulmonary infarction should be considered seriously. Pulmonary infarction not infrequently presents in this way. The history is not always characteristic and may actually suggest a chronic disease process. These 6 case reports have been presented to illustrate the manifold and unusual manifestations in which pulmonary infarction may present both clinically and roentgenographically. Since pulmonary infarctions are apparently becoming more frequent and are associated with such serious consequences and high mortality, it is important to bear in mind their unusual features.

Summary

It is difficult to diagnose pulmonary infarction by roentgenographic or clinical findings alone, but increased difficulty occurs when the clinical and roentgenographic appearances are unusual or bizarre. Rounded densities and abnormalities of the upper lobes on roentgenograms of the chest do not exclude the possibility of pulmonary infarction. Reports on 6 patients with unusual clinical and roentgenographic manifestations of pulmonary infarctions are presented. With the increased incidence of pulmonary infarction and embolism, and their serious import, the unusual as well as the usual clinical presentations must be known.

Sumario

Extrañas Características Clínicas y Radiográficas del Infarto Pulmonar

Es difícil diagnosticar el infarto pulmonar exclusivamente por los hallazgos roentgenográficos o clínicos, pero aun más cuando los aspectos clínico y radiográfico son extraños o caprichosos. Las condensaciones y anomalías redondas de los lóbulos superiores en las radiografías torácicas no excluyen la posibilidad de infartos pulmonares. Se presentan informes de 6 enfermos que tenían extrañas manifestaciones clínicas y roentgenográficas de infartos pulmonares. Dada la mayor incidencia del infarto y de la embolia pulmonares, y su grave significado, hay que conocer las manifestaciones extrañas así como las habituales.

Resume

Traits radiographiques et cliniques inhabituels d'infartus du poumon

Il est difficile de diagnostiquer un infarctus pulmonaire rien que par les données cliniques ou radiographiques, mais la difficulté s'accroit lorsque le tableau clinique ou radiographique est inhabituel ou bizarre. Des densités rondes et des anormalités des lobes supérieurs dans les radiographies de la poitrine n'excluent pas la possibilité d'infarctus pulmonaires. Les auteurs présentent les histoires de 6 malades ayant des manifestations cliniques et radiographiques inhabituelles d'infarctus du poumon. Il faut être au courant des formes cliniques habituelles aussi bien qu'inhabituelles, avec la fréquence croissante des emboli et des infarctus pulmonaires et de ce qu'il comporte de sérieux.

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FAMILIAL SPONTANEOUS PNEUMOTHORAX[1]

VERA LEITES AND ELK TANNENBAUM

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INTRODUCTION

Familial spontaneous pneumothorax is a rare condition. In a recent publication on the subject, Boyd (1) in 1957 reviewed 21 cases reported in the literature up to that time and added three cases of his own. Two other cases were described in 1956 in the Spanish literature (2). These twenty-six cases of spontaneous pneumothorax were encountered in twelve families; in eight families, spontaneous pneumothorax was found in siblings; in the remaining four families, it occurred in a father and son or father and one or two daughters. There were approximately twice as many males with spontaneous pneumothorax as females in these families. The most plausible explanation for this condition according to Boyd is the rupture of congenital, hereditary lung cysts. Since multiple cases of spontaneous pneumothorax in a single family are obviously unusual, the following reports should be of interest.

CASE REPORTS

Three brothers, *T. G.*, *J. G.*, and *W. G.*, 24, 22, and 21 years old, respectively, had been patients of one of the authors (E. T.) since early childhood. They were referred by him to a Health Department chest clinic because of clinical symptoms suggestive of spontaneous pneumothorax. Family history revealed that the mother has been a patient in a mental hospital for many years. The father is apparently in good health. Of the four sons of this marriage, the youngest two are deaf-mutes.

Case 1. T. G., 24 years old, was referred to the chest clinic in April, 1957, because of chest pain and dyspnea. A roentgenogram revealed approximately a 20 per cent collapse of the left lung. He was referred for admission to a hospital where a left parietal pleurectomy was performed. At operation small subpleural blebs were found in the left upper lobe. The patient has been well and working since.

Case 2. J. G., 22 years old, with a marked pectus excavatum, was referred to the chest clinic in March, 1957, because of right chest pain. He had had one episode of spontaneous pneumothorax one year previously. An admission chest roentgenogram showed approximately a 10 per cent collapse of the right lung. There was complete re-expansion after ten days of rest. Sixteen months later he was referred to the clinic again with a spontaneous pneumothorax on the left side. He was admitted to a hospital where a bilateral pleurectomy was performed, with resection of a bleb of the left upper lobe. The patient has been well and working since then.

Case 3. W. G., 21 years old, a deaf-mute, was referred to the chest clinic in October, 1959, because of left chest pain and dyspnea. A roentgenogram revealed a complete collapse of the left lung. This was apparently the first episode of spontaneous pneumothorax in this patient. He was referred to a hospital where a left parietal pleurectomy was performed. Small blebs were found in the left apex.

J. G. the youngest brother, 18 years old, a boarder in an institution for the deaf, had negative survey roentgenograms in 1952 and 1957 and allegedly has shown no clinical indication of spontaneous pneumothorax.

SUMMARY

The cases of 3 brothers with spontaneous pneumothorax are reported. Two brothers had recurrent episodes of collapse. In all 3, operation revealed the presence of subpleural blebs. These might possibly be of congenital origin. Other definitely congenital anomalies among the 4 brothers in the family are deaf-mutism in 2 and pectus excavatum in one.

SUMARIO

Neumotórax Espontáneo Familiar

Preséntanse los casos de 3 hermanos que tenían neumotórax espontáneo. Dos hermanos tuvieron episodios recurrentes del aplastamiento. En los 3, la operación reveló la existencia de flictenas subpleurales. Estas podían posiblemente reconocer origen congénito. Otras anomalías seguramente congénitas entre los 4 hermanos de la familia son sordomudez en 2 y *pectus excavatum* en uno.

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Resume

Pneumothorax familial spontané

Les auteurs rapportent les cas de 3 frères ayant un pneumothorax spontané. Deux frères présentèrent des rechutes de collapsus. Chez tous les trois, l'opération révèla la présence de bulles sous pleurales. Celles-ci pourraient être d'origine congénitale. Chez 4 frères de cette famille, il y a d'autres anomalies surement congénitales: deux cas de surdimutité et un cas de pectus excavatum.

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Notes

COMPARATIVE STUDY OF ISONIAZID VERSUS NO CHEMOTHERAPY IN THE PREVENTION OF RELAPSE OF CHRONIC CAVITARY TUBERCULOSIS

It is commonly accepted practice to continue isoniazid treatment indefinitely in cases of chronic pulmonary tuberculosis for its "holding action" against relapse. The patients usually selected have stabilized cavitary tuberculosis with sputum which contains or has contained tubercle bacilli resistant to the two major antituberculous drugs, and frequently also to the secondary drugs. Surgical treatment is impossible or refused by the patient. The writers have been unable to find in the literature any studies which would prove that isoniazid has such a prophylactic action in preventing relapse in such patients. Since this hospital admits transfers from various Philadelphia hospitals, patients with several previous hospital admissions, and many considered as previous treatment failures, the writers have been interested in this problem

Accordingly, a number of such patients were selected and divided into two groups by random numbers. All but one of these patients had received isoniazid previously in multiple-drug therapy for periods ranging from 3 to 48 months, and averaging 21 months. Seven patients had also received isoniazid alone, as well as in combination, at one time or another for periods ranging from one month to 9 months, and averaging 4.6 months. Most of the patient-strains of tubercle bacilli (34 of the 47)) were resistant to isoniazid concentrations of 5γ per ml. at the beginning of the study. Only 5 were still susceptible to this concentration of isoniazid. Unfortunately, it was not possible to obtain resistance studies on 8 of the patient-strains because the organisms failed to grow on culture. The sputum from all but one of these patients was negative for tubercle bacilli on microscopy. Thirty-two of the patients had organisms demonstrable by microscopy or culture, and the secretions of 15 were negative on both microscopy and culture at the time of selection.

After the groups were selected they were found to be comparable on the basis of age, race, cavitation, infectious sputum, catalase reaction, and stage of the disease. They were all males. One of the groups was selected by chance to receive isoniazid alone while the other group received all the treatment the first group received such as high caloric diet, bed rest, and symptomatic care, but did not receive any specific antimicrobial therapy against tuberculosis. Patients weighing less than 150 pounds received 300 mg. of isoniazid daily while those weighing more than 150 pounds received 400 mg. per day. The range was from 4 to 7.5 mg. per kg. of body weight per day. At the end of a year the two groups were compared and the results were tabulated.

The results as to roentgenographic relapse or worsening are tabulated in table 1. Roentgenographic relapse was defined as any of the following: (*1*) spread of the disease to a new area; (*2*) definite worsening or increase in disease in a previous area of disease; (*3*) appearance of a cavity where there had been none before, or (*4*) significant enlargement of a cavity with an increase in the focal reaction surrounding it. It may be seen from the table that there were six roentgenographic relapses in the "isoniazid alone" group of 21 patients and ten roentgenographic relapses in the 26 patients serving as controls. The difference between the groups is not statistically significant (chi-square = 0.448 and P = 0.50).[1] While the control group with roentgenographic relapse had shown this early in the course of the study at an average of 4 months, those of the "isoniazid alone" group who relapsed averaged 6 months before their adverse break.

TABLE 1

ROENTGENOGRAPHIC AND BACTERIOLOGIC RELAPSE IN TUBERCULOUS PATIENTS WHO RECEIVED ISONIAZID ALONE COMPARED WITH NO ANTIMICROBIAL THERAPY

Patient Groups	Number of Patients	Roentgenographic Relapses	Bacteriologic Relapses	Bacterial "Conversion" to Negative
Isoniazid	21	6	2	1
Nonspecific care	26	10	1	2

There were two bacteriologic relapses and one reversal of infectiousness in the "isoniazid alone"

[1] Statistical analysis was performed by Mr. William J. Carnahan, Statistician to the Philadelphia Tuberculosis and Health Association.

group, while there was one bacteriologic relapse and two "conversions" in the control group. These figures are too small to have any significance.

A point of side interest is that there were 25 patients in the study who had catalase-negative and isoniazid-resistant tubercle bacilli. Ten of these patients had roentgenographic relapses. There were 4 in the "isoniazid alone" group and 6 in the control group, dispelling any confidence that tuberculous patients with isoniazid-resistant and catalase-negative tubercle bacilli are safe from relapse.

In summary: In a relatively small study, there was no statistically significant difference in roentgenographic relapse between a group of patients with stabilized pulmonary tuberculosis who received isoniazid alone compared with a similar group receiving no antimicrobial therapy. A significant number of the relapses occurred in patients harboring isoniazid-resistant, catalase-negative tubercle bacilli.

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January 26, 1960

RESPONSE OF MONKEYS TO RESPIRATORY CHALLENGE FOLLOWING SUBCUTANEOUS INOCULATION WITH COCCIDIOIDES IMMITIS[1]

Subcutaneous injection of virulent *Coccidioides immitis*, strain Silveira, into white mice results in a localized abscess, and it was indicated that the animals so treated showed increased resistance to subsequent intraperitoneal or intranasal challenge with virulent *C. immitis*.[2] The resistance of mice to subcutaneously induced infection is in marked contrast to infection of this highly susceptible host by other routes. These findings are in agreement with sporadic reports of other attempts to infect animals (and humans) through the skin. Furthermore, in two well-documented cases,[3, 4] humans accidentally infected by percutaneous inoculation of *C. immitis* incurred relatively benign infections. It was decided, therefore, to study comparatively the response of the cynomolgous monkey (*Macacus irus*) to subcutaneous inoculation of *C. immitis* and to subsequent respiratory challenge with *C. immitis*.

Seven monkeys constituted the experimental group which received subcutaneous inoculation. Four additional monkeys were used as controls. These animals, obtained from the Philippines, were of both sexes and mixed sizes from approximately 2 to 4 kg. in weight. Each was housed in a separate cage.

The site of subcutaneous inoculation chosen was the interscapular region because it is the least accessible to the hands of the monkey. An area 2 to 4 cm. in diameter was manually depilated. A suspension of *C. immitis*, strain Silveira, arthrospores in 0.85 per cent sodium chloride was administered with a tuberculin syringe fitted with a 23-gauge needle. Monkeys Nos. 1 and 5 received 500 spores in 0.5 ml. with a resultant bleb. Monkeys Nos. 2, 3, 4, 6, and 7 were given 100 spores in 0.1 ml. volume which produced no visible swelling. Because of difficulty in handling and the possibility that the local site might be unduly traumatized, the monkeys were removed from their individual cages only four, eight, sixteen, and fifty-two days after inoculation for observation of the local site of inoculation.

At seventy-three days after subcutaneous inoculation, the 7 experimental animals and 4 normal control monkeys were subjected to respiratory challenge with an aerosol of *C. immitis*, strain Silveira. The respiratory exposure was accomplished in the monkey exposure unit previously described by Miller.[5] Some of the animals (Nos. 1, 3, 4, 5, and controls Nos. 8, 9, 10, 11) inhaled 746 arthrospores (calculated dose), and the remainder (Nos. 2, 6, 7) inhaled 2.9×10^4 spores (table 1).

Lateral view chest roentgenograms ($8\frac{1}{2}$ in. $\times$ 11 in.) were taken on the same day as subcutaneous inoculation sixteen days later, one day prior to respiratory challenge and thirty-five days after respiratory challenge.

Blood for serologic tests (complement-fixation) was taken by cardiac puncture just prior to sacrificing the animals with sodium pentobarbital.[6]

Monkey No. 1 was considered moribund at forty-one days after respiratory challenge and was therefore sacrificed. The remaining animals were sacrificed forty-six days following respiratory challenge. At autopsy the gross appearance of organs was noted and portions were removed into Technicon fixative FU-48. After embedding in paraffin, the tissues were sectioned, then stained with Giemsa stain and the periodic acid-Schiff stain of Kligman and Mescon.[7]

The lesion at the local site first became evident at four days after subcutaneous inoculation in those monkeys (Nos. 1 and 5) inoculated with 500 spores as an indurated area 1 cm. in diameter and with little erythema. Slight induration was also noted in monkeys Nos. 4 and 6 at this time.

After eight days, each animal had developed a turgid, swollen nodule, movable under the skin. On monkey No. 1 (500-spore inoculum), the local site was approximately 3.5 cm. in diameter and 0.5 cm. high, while in the other animals the diameter of the lesion was 1 to 2 cm.

By sixteen days after inoculation, the lesions were 1.5 to 3 cm. in diameter, slightly erythematous, fluctuant, and with a hard base. A slight amount of creamy pus oozed from the lesions of Nos. 3 and 4, probably due to their trauma incurred during capture of the animals for inspection. Animal No. 1 showed two satellite fluctuant nodules, each 4 cm. in diameter and raised 2 cm. above the general surface of the skin.

[1] This work was supported by the Bureau of Medicine and Surgery, U. S. Navy, and the Office of Naval Research under a contract with the Regents of the University of California. Opinions contained in this report are not to be construed as reflecting the views of the Naval Service.

[2] Pappagianis, D., *et al.*: J Invest Derm, 1959, *32*, 589.

[3] Wilson, J. W., *et al*: Calif Med, 1953, *79*, 233.

[4] Trimble, J. R., and Doucette, J.: AMA Arch Derm, 1956, *74*, 405.

[5] Miller, R. L., and Nees, W. E.: Unpublished observations, 1957.

[6] Beuthanasia, H. C. Burns Co., Oakland, California.

[7] Kligman. A. M., and Mescon, H.: J Bact, 1950, *60*, 415.

TABLE 1

SUBCUTANEOUS INOCULATION OF MACACUS IRUS WITH COCCIDIOIDES IMMITIS FOLLOWED BY RESPIRATORY CHALLENGE

Animal Number	Dose		Chest Roentgenogram*	Condition at Sacrifice	Complement-Fixation Titer
	Subcutaneous	Respiratory			
1	500	746	Clear	Cachectic, moribund	512
2	100	2.9×10^4	Clear	Cachectic, weak	8
3	100	746	Clear	Strong	128
4	100	746	Clear	Strong	64
5	500	746	Clear	Strong	128
6	100	2.9×10^4	Clear	Cachectic, weak	—
7	100	2.9×10^4	Clear	Strong	256
			Controls		
8	0	746	Diffuse nodular densities, 5–6 mm.	Cachectic, weak	64
9	0	746	Diffuse nodular densities, 5–6 mm.	Cachectic, weak	4
10	0	746	Widespread diffuse infiltrate	Cachectic, weak	<2
11	0	746	Massive diffuse infiltrate	Cachectic, weak	8

* Roentgenograms taken thirty-two or thirty-five days post respiratory exposure.

When examined at fifty-two days, the lesions were still 2 to 3 cm. in diameter, but in animals Nos. 2, 3, 4, 5, and 6 a small scab capped the site; beneath, the lesions were fluctuant. In monkey No. 1 the lesion appeared to extend 4 to 5 cm. toward the left arm; this limb was weak and favored by the monkey. With this exception, the vigor and fugaciousness of the monkeys were undiminished.

At the time of respiratory challenge (seventy-three days after subcutaneous inoculation), the subcutaneous lesions remained swollen and slightly fluctuant centrally, with peripheral induration.

The pulmonary roentgenograms of the experimental and control monkeys were strikingly different thirty-five days after respiratory challenge. The control animals showed massive fluffy infiltrates with widespread diffuse nodular densities (Plate I, Nos. 9 and 11). On the other hand, there were virtually no abnormal markings in the roentgenograms of the monkeys with prior subcutaneous inoculation (Plate I, Nos. 2 and 5). The differences in severity evidenced by roentgenograms were paralleled in the hisologic findings to be described below. Clinically, all 4 animals of the control group were cachectic and extremely weak. The physical condition of the experimental group was not so uniform. Monkey No. 1 previously has been described as moribund when sacrificed forty-one days after challenge. Monkeys Nos. 2 and 6 were very weak and cachectic, but Nos. 3, 4, 5, and 7 were strong and energetically avoided capture. Thus, while a dose of 746 arthrospores was manifestly detrimental to the control animals, three of the four experimental groups resisted that challenge. Indeed, one of 3 monkeys remained strong despite challenge with 2.9×10^4 spores.

The regularity of the pulmonary roentgenographic lesions of each group was mirrored in the gross and microscopic findings. The lung tissue of the control monkeys contained many relatively large tubercles (up to 5 mm. and often confluent) of Huntington's[8] "micro-abscess granuloma mixture." These lesions are evident in Plate II (Nos. 8 through 11). Histologic examination showed multinucleate giant cells and large central necrosis. The lesions contained many immature spherules (8 to 30μ) and some with endospores (Plate III, Nos. 8 and 10). Peripheral to these areas in which the normal alveolar structure was destroyed or not discernible, there were extensive collections of mononuclear cells in exudate in alveoli whose normal configuration was essentially unchanged. When the tubercles lay immediately subjacent to the pleura, the latter was much thickened.

The strikingly different appearance of the previously infected animals may be seen in Plate II. There were infrequent, small (0.1 to 0.7 mm.) punctate lesions visible in lung sections of monkeys Nos. 2, 4, 6, and 7. Even these were absent in the sections examined from monkeys Nos. 3 and 5. The tissue from monkey No. 1 contained

[8] HUNTINGTON, R. W., JR.: U. S. Public Service Publication, 1957, *575*, 36.

more punctate nodules, and some were actually confluent. Histologically, the absence of necrosis and the paucity of Coccidioides cells were especially notable.

Despite the absence of necrosis, conspicuous changes of lung structure were generally evident. These consisted of thickening of alveolar walls by inflammatory cells and hyperemic alveolar capillaries. Partially atelectatic areas were seen, and in some areas fluid exudate or blood was present in the alveolar spaces. In some alveoli loose collections of large mononuclear cells could be seen. As shown in Plate III (No. 7) the visible lesions referred to above consisted of a circular aggregate with Langhans' or foreign-body giant cells and numerous other epithelioid cells centrally situated. Centrifugally there were great numbers of other mononuclear cells and lymphocytes. Only occasionally were nuclei or fragments of nuclei of polymorphonuclear leukocytes conspicuous within these lesions. Encapsulation of the lesions was not prominent, although in some areas circumferential fibroblasts were found. While some of the inflammatory cells seemed to overflow into adjacent structures, the alveolar walls often remained discernible within lesions.

In the experimental group, the few *C. immitis* cells were immature spherules 12 to 20μ in diameter contained within the cytoplasm of giant cells (Plate III, No. 7). This rarity of spherules in the monkeys of the experimental group was in outstanding contrast to the multiplicity of fungous bodies in the controls (Nos. 8 and 10, figure 3). Application of the periodic acid-Schiff stain strikingly confirmed the abundance of *Coccidioides* cells in lesions of the control animals and their virtual absence from lesions of the experimental group.

Small nodular lesions were observed in the liver and spleen in some but not in all animals of both groups, appearing more numerous in organs of the control animals. In these visceral lesions, *C. immitis* cells were sparse.

Results of the complement-fixation tests are also shown in table 1. It is evident that, with the exception of monkey No. 2, the serum titers were higher in the group which had received prior subcutaneous inoculation than in those without prior subcutaneous inoculation. Unfortunately, no prechallenge specimens of serum were taken with which these could be compared.

* * *

In general, the response of the monkeys to subcutaneous inoculation of *Coccidioides immitis* appeared in the form of a localized abscess as previously reported for the mouse.[2] However, in contrast to the latter host in which 100 arthrospores of strain Silveira produced a lesion usually less than 5 mm. in diameter, this same dose of arthrospores produced large fluctuant abscesses up to 3 cm. in diameter. This may signify a lesser local tissue resistance in the subcutaneous region in the monkey. Posadas[9] recorded this low resistance of the monkey inoculated subcutaneously with material from coccidioidal lesions of a human; however, his animal died following early dissemination from the local site.

The subsequent respiratory challenge indicated enhanced resistance, evidenced from both roentgenographic and histopathologic observations. Notwithstanding these encouraging findings, the severe illness seen in some of the experimental animals was no less dismaying than in the controls. Possibly, intercurrent infection was contributory, but examination of tissue sections revealed no evidence of secondary infection. Another possibility may have been that the interval between the subcutaneous inoculation and the respiratory challenge was too short so that the effect was that of a single overwhelming superinfection. Neither roentgenographic nor histopathologic evidence revealed clues for differentiating the clinical responses of the monkeys in the experimental group. The apparent absence of paralytic central nervous system involvement does not completely exclude such lesions, while allergic or endocrine phenomena also might be responsible.

The persistent good health of over half of the infected-challenged animals invites a variety of modifications for future experiments: the use of a nonvirulent strain for subcutaneous inoculation; a longer interval between "immunization" and challenge; or the employment of a smaller dose for the respiratory challenge, since the monkey may be an inordinately susceptible host.

The higher complement-fixing titer seen in those animals which resisted respiratory challenge at first glance might seem discordant since experience with human coccidioidal infections has indicated direct correlation between high titer and severity of disease.[10] However, the prior subcutaneous inoculation possibly led to an early complement-fixing antibody response, with a later "booster" stimulus from the respiratory challenge. Moreover, the serologic response of monkeys is not well studied.

It is perhaps of interest here to note the greater resistance of cynomolgous monkeys to primary respiratory (intratracheal) challenge with *Histoplasma capsulatum* as found by Hill and Marcus.[11] The latter writers found that a challenge dose of

[9] Posadas, A.: Rev Chir (Paris), 1900, *21*, 277.
[10] Smith, C. E., *et al.*: Am J Hyg, 1950, *52*, 1.
[11] Hill, G. A., and Marcus, S.: Amer Rev Tuberc, 1957, *75*, 849.

2×10^7 Histoplasma cells did not cause illness during a six-month observation period, whereas the severe illness was caused by 750 Coccidioides spores.

In summary: Seven monkeys were inoculated subcutaneously with viable spores of *Coccidioides immitis* of virulent strain Silveira. Five of these animals received 100 spores; 2 received 500 spores. At the site of inoculation a large fluctuant absces developed to maximal size (about 2 to 3 cm.) in two weeks. This lesion appeared to remain localized in all but one monkey, in which infection spread to the left arm.

The 7 experimental animals, plus 4 control monkeys, were subjected to inhalatory challenge with *C. immitis* spores of strain Silveira. The controls received a calculated dose of 746 organisms. Four of the experimental group received 746 spores, while the remaining 3 animals received 29,000 spores.

Widespread coccidioidal disease developed in the control monkeys which were severely ill when sacrificed at forty-six days after respiratory challenge. Roentgenograms and subsequent autopsy revealed massive pulmonary involvement. Histopathologic examination demonstrated a profusion of *C. immitis* spherules in the large mixed granulomatous lesions with extensive necrosis. These were often 1 cm. or greater in size, and frequently confluent.

The previously infected monkeys gave a mixed response to the respiratory challenge with *C. immitis*. Of the 6 which appeared to localize the subcutaneous inoculum, 3 were healthy and 3 were very ill when sacrificed forty-six days after challenge. Despite this difference in state of health, the roentgenographic and histopathologic findings were very similar. The development of *C. immitis* was strikingly restricted to only rare immature spherules. The pulmonary lesions were similarly restricted (0.1 to 0.7 mm. in diameter), widely scattered, and rare in some cases. Necrosis was virtually absent. Pneumonitis with edema fluid and occasional hemorrhage was present. Roentgenographic or histopathologic findings in 2 of the experimental group of monkeys which became severely ill did not contain features distinctive from those observed in the healthy animals.

Evaluation of the subcutaneous inoculation as a procedure for immunization of monkeys against respiratory challenge with *C. immitis* was made difficult because of the mixed response in such a small group of experimental animals. However, prior experience with viable subcutaneous *C. immitis* appeared to provide resistance to *C. immitis* in respiratory challenge.

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February 23, 1960

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[13] The writers wish to thank John Schutz and Richard Werre, PH (G)3, USN, for preparation of the photographs included in this report.

(*Plates I, II, and III on following pages*)

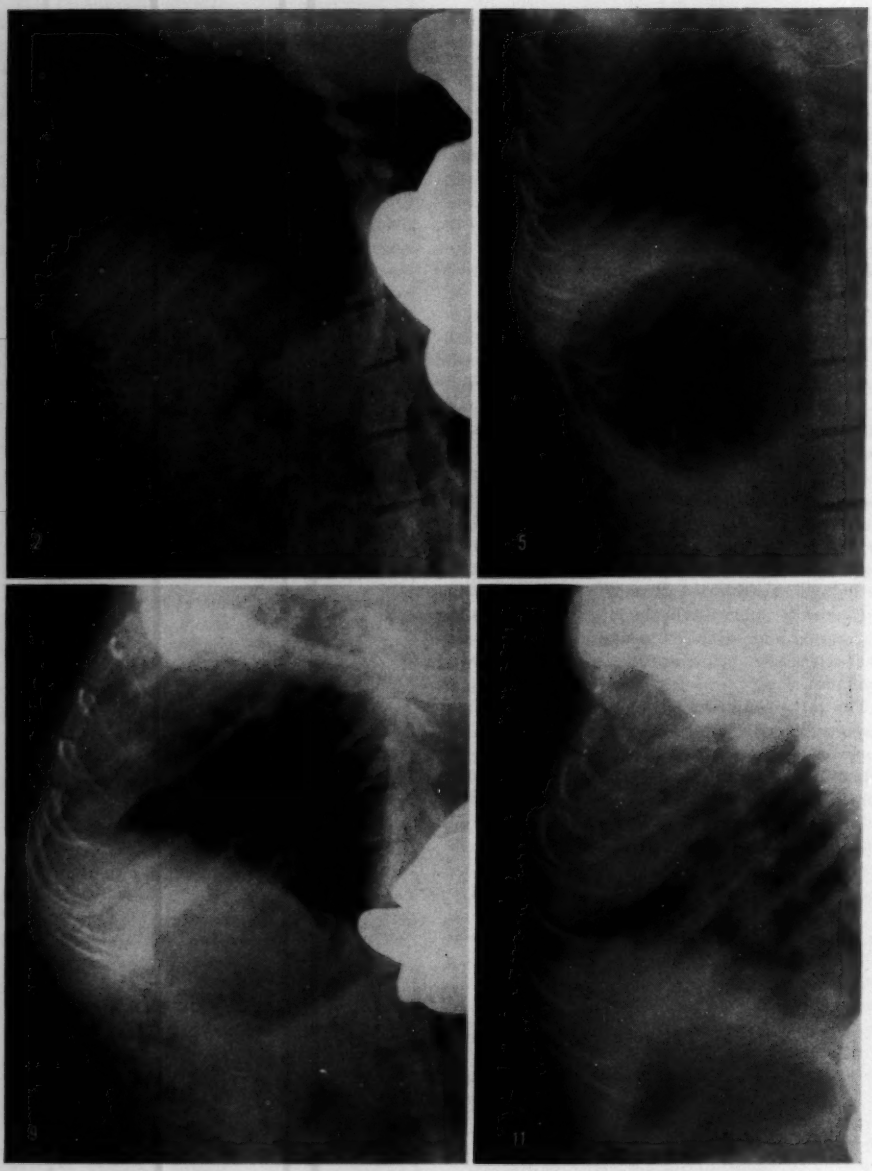


PLATE I

Lateral roentgenograms of monkeys thirty-five days after respiratory challenge with spores of *Coccidioides immitis*. Monkeys Nos. 2 (upper left) and 5 (upper right) had been previously inoculated subcutaneously with viable *C. immitis*. Monkeys Nos. 9 (lower left) and 11 (lower right) were not previously inoculated subcutaneously.

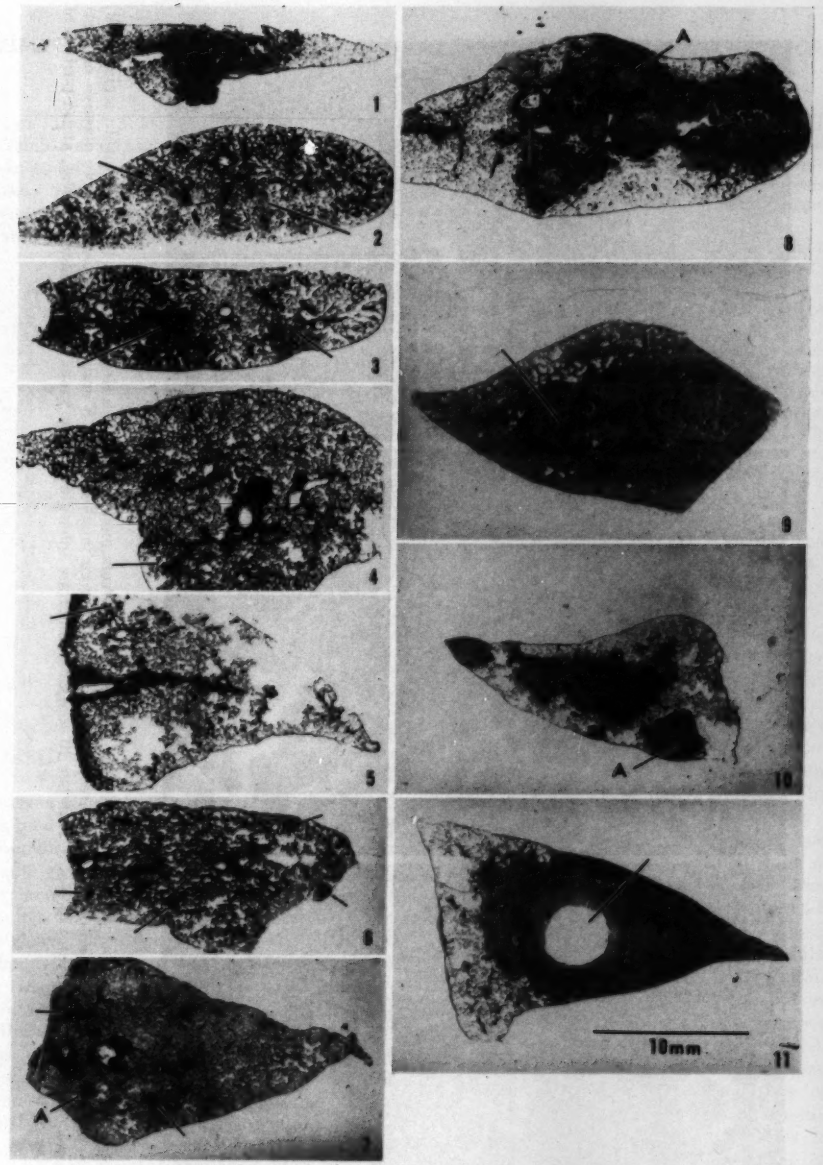
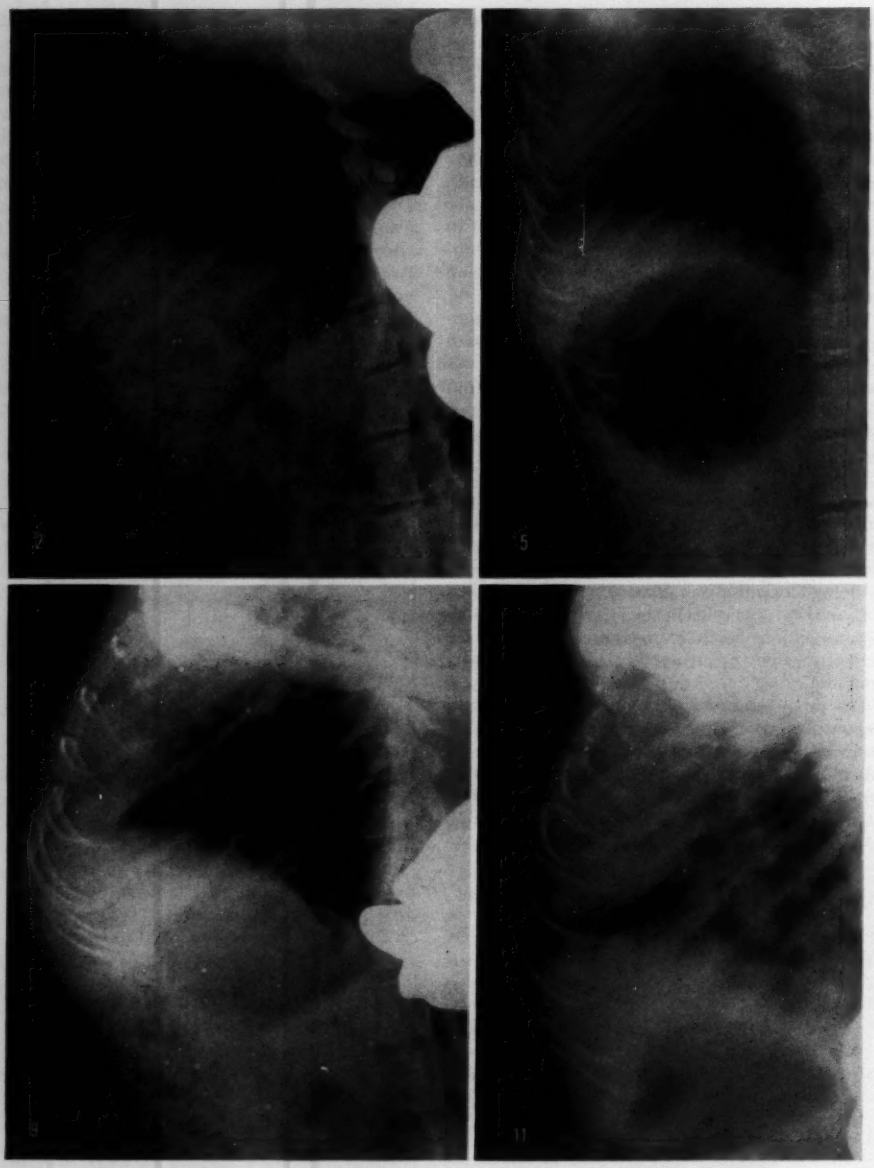


PLATE II

Stained sections of lungs of monkeys forty-six days after respiratory challenge with *Coccidioides immitis*. On the left are tissues from animals previously inoculated subcutaneously. On the right are tissues from control animals. Note large caseous lesions of latter compared with smaller tubercles of those on left. (All approximately 2×, Giemsa stain)



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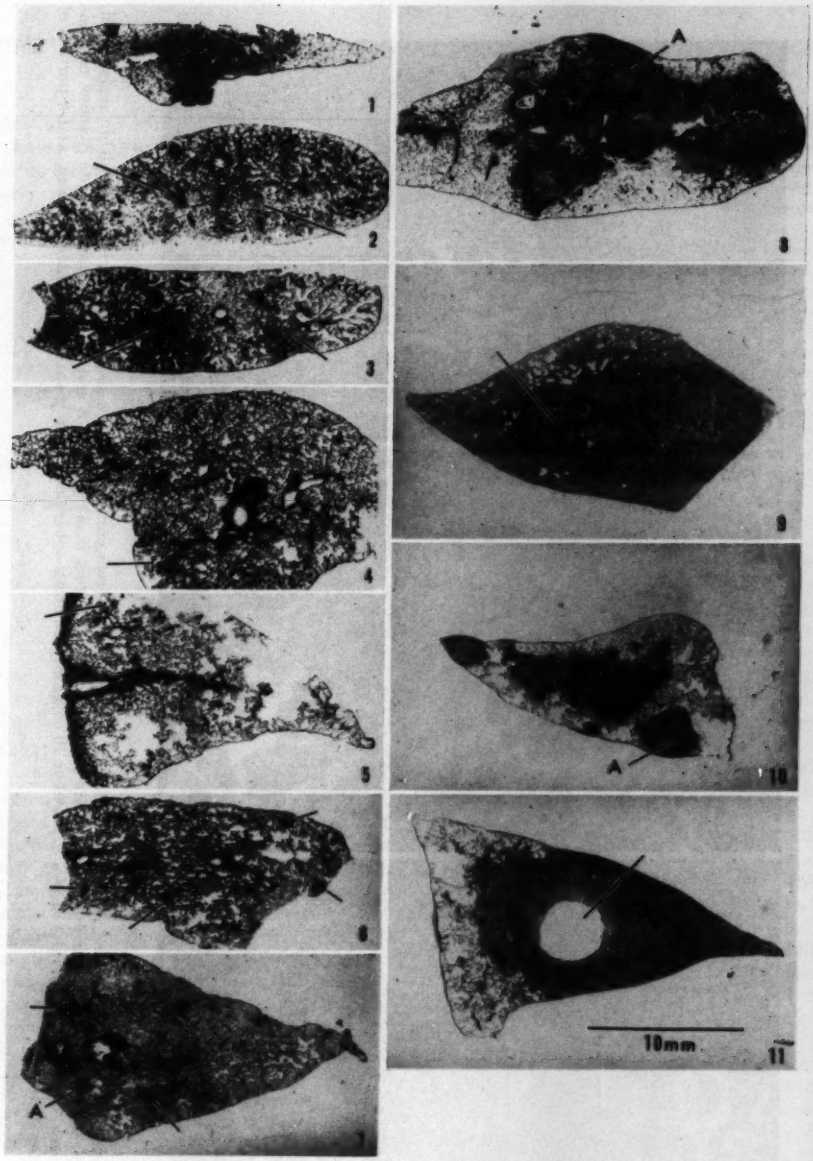

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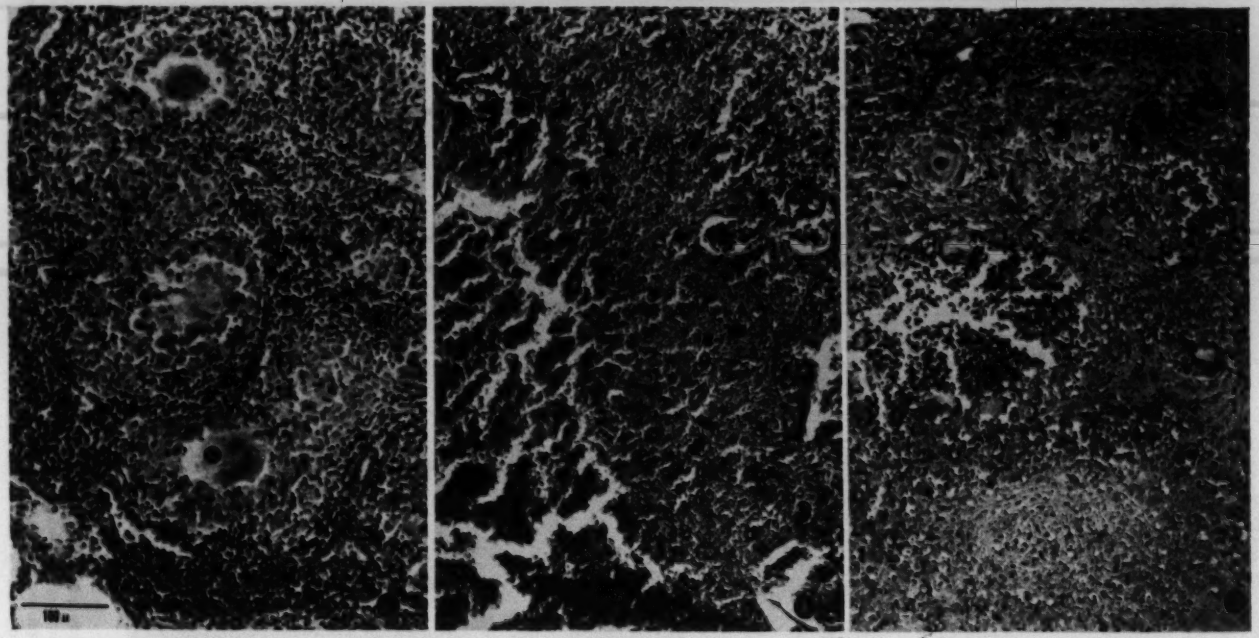
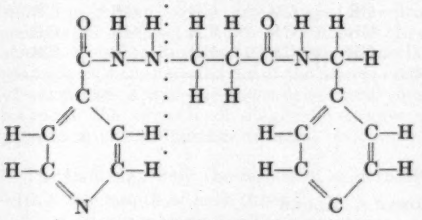


PLATE III

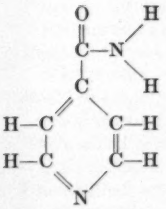
Higher power view of lung areas marked *A* in figure 2. On the left is tubercle from monkey No. 7: a single spherule is visible within a giant cell, necrosis is inconspicuous. In the middle and on the right are portions of lesions from monkeys Nos. 8 and 10, respectively. Note massive necrosis and many endospores of immature spherules in No. 8. Number 10 contains numerous spherules within giant cells, a micro-abscess, and a portion of large necrotic center of lesion.

ANTIMYCOBACTERIAL ACTIVITY OF *N*-ISONICOTINYL HYDRAZIDE AND CROSS RESISTANCE TO ISONIAZID

A new drug, *N*-isonicotinyl-*N'*-(B-*N*-benzyl-carboxamido-ethyl)-hydrazine, recently put on the market for the treatment of mental depression is closely related chemically to isoniazid. The chemical structures of the *N*-isonicotinyl hydrazide and isoniazid are as follows:



N-isonicotinyl hydrazide



ISONIAZID

Because a molecule of *N*-isonicotinyl hydrazide is composed of a molecule of isoniazid with a substitution for one of the hydrogen atoms in the prosthetic group, as indicated by the dotted line, it was thought that the drug might possess antituberculous as well as psychic activity. If *N*-isonicotinyl hydrazide does inhibit tubercle bacilli, its administration to psychiatric patients with active tuberculosis might result in the development of resistance of the bacteria to isoniazid, thus eliminating the effectiveness of this drug for subsequent therapy of the tuberculosis. Further ramifications of this situation would include cross infection of other psychiatric patients with isoniazid-resistant tubercle bacilli, but need not be explored here.

A series of *in vitro* tests has been conducted to determine whether *N*-isonicotinyl hydrazide possesses antimycobacterial activity. The possibility that tubercle bacilli resistant to isoniazid might be cross resistant to *N*-isonicotinyl hydrazide *in vitro* was also investigated.

Three cultures of acid-fast bacilli susceptible to 0.1γ of isoniazid and three cultures resistant to 5.0γ of isoniazid per ml. of medium were used to test for susceptibility and cross resistance studies. The cultures were recent isolations from patients hospitalized for tuberculosis.

A sample of pure *N*-isonicotinyl hydrazide was obtained.[1] The drug was incorporated into Löwenstein-Jensen medium in the following concentrations: 0.01, 0.1, 1.0, 5.0, 20, and 100γ per ml. of medium. Isoniazid susceptibility tests were performed simultaneously at concentrations of 0.1, 1.0, and 5.0γ per ml. of the same medium.

The bacteria were emulsified in physiologic saline, and approximately one billion organisms were inoculated onto each medium slant. Control tubes of Löwenstein-Jensen medium without drug were also used. The cultures were read at twenty-eight days.

The results, as given in table 1, show that the *N*-isonicotinyl hydrazide does indeed have antimycobacterial activity, since it completely inhibited the growth of isoniazid-susceptible organisms at concentrations of 1γ per ml. of medium, or more. It should also be noted that the *N*-isonicotinyl hydrazide did not inhibit growth at 0.1γ per ml., although isoniazid was effective at this level. The results also show that, when the tubercle bacilli were completely resistant to 5.0γ of isoniazid, they were also completely resistant to the same concentration of *N*-isonicotinyl hydrazide and to concentrations as high as 100.

The higher minimal *in vitro* inhibitory concentration of the *N*-isonicotinyl hydrazide, as shown in the results, can be accounted for by the fact that its molecular weight (297.3) is about 2.4 times that of isoniazid (125.1). Assuming that only the isoniazid part of the molecule exerts an inhibitory effect on the tubercle bacilli, the lesser effectiveness of *N*-isonicotinyl hydrazide would result from the fact that the drugs were incorporated in the medium in terms of weight.

When *N*-isonicotinyl hydrazide is administered to a psychiatric patient, diagnostic studies for the presence or absence of tuberculosis should be carried out and the status of its activity determined. If active tuberculosis is present, a second antimycobacterial drug should also be given in accordance with the currently established prin-

[1] Kindly supplied as Niamid by Pfizer Laboratories, Medical Department, 630 Flushing Avenue, Brooklyn 6, New York.

TABLE 1

SUSCEPTIBILITY STUDIES ON ISONIAZID AND *N*-ISONICOTINYL HYDRAZIDE

Culture Source	Control	Isoniazid			*N*-Isonicotinyl Hydrazide					
		γ/ml.			γ/ml.					
		0.1	1.0	5.0	0.01	0.1	1.0	5.0	20	100
E	4+	S	S	S	CR	CR	S	S	S	S
G	4+	S	S	S	CR	CR	S	S	S	S
P	4+	S	S	S	CR	CR	S	S	S	S
K	4+	CR	CR	CR	CR	CR	CR	CR	CR	CR
R	4+	CR	CR	CR	CR	CR	CR	CR	CR	CR
S	4+	CR	CR	CR	CR	CR	CR	CR	CR	CR

Key:
4+ = confluent growth over entire medium surface.
S = no growth.
CR = same as 4+.

ciples of multiple-drug therapy for tuberculosis.

The "psychic energizing" drug, *N*-isonicotinyl hydrazide, possesses antimycobacterial activity because its structure includes a molecule of isoniazid. When tubercle bacilli are resistant to isoniazid, they are also cross resistant to the isonicotinyl compound.

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March 1, 1960

PAIRED SPUTUM AND GASTRIC WASHING CULTURES

This is a review of 1,207 paired cultures of sputum and gastric washings on patients receiving chemotherapy. It was compiled in an attempt to determine the efficiency of using gastric washings in patients whose sputum volume is scant under the influence of chemotherapy.

The chemotherapy record cards were reviewed, starting from 1953. Beginning with the third month of chemotherapy only the sputum cultures and gastric washing cultures occurring within one month of each other were tabulated. In the large majority of instances the use of the double method of examination was due to scant sputum volume although the variable of diagnostic studies was present in a small number of cases.

The following were the results of examinations within one month of each other:

Negative for tubercle bacilli on sputum and gastric washing cultures	1,176
Positive for tubercle bacilli on both sputum and gastric washing cultures	13
Positive for tubercle bacilli on sputum culture only	10
Positive for tubercle bacilli on gastric washing culture only	8
Unclassified mycobacterial cultures by both methods	0
Unclassified mycobacteria on sputum culture only	0
Chromogenic and unclassified mycobacteria on gastric washing culture only	10
Sputum positive for tubercle bacilli on microscopy when both cultures were negative (2 of the 18 were unclassified)	18

The yield of only 8 gastric washing cultures positive for tubercle bacilli alone in patients whose sputum was scant under the influence of chemotherapy did not justify the additional 1,207 examinations required. The use of gastric washing cultures in this type of patient increased the workload, as there were 10 chromogenic and other unclassified mycobacterial cultures requiring further investigation.

Probably, increasing the number of sputum cultures (perhaps sputum smears) would have been as effective as gastric washings in evaluating sputum "conversion" under the influence of chemotherapy. Superficially, the positive smear–negative culture problem was not great; but the series is inaccurate for judging this problem, as frequently it was the negative smears which caused the physician to question the adequacy of sputum volume and to order gastric washings.

The study did not investigate the efficiency of gastric washing cultures on admissions, but it can be implied that sputum examinations in the presence of an adequate sputum volume can be accepted as reliable if the number of examinations is adequate. The results of gastric washing cultures when the sputum volume was too low for sputum cultures was not investigated and nothing can be inferred.

W. E. Roye
Veterans Administration Hospital
Richmond 19, Virginia

March 30, 1960

Correspondence

TRACHEAL PUNCTURE TO OBTAIN LOWER RESPIRATORY TRACT SECRETIONS

To the Editor of The American Review of Respiratory Diseases:

We have read with interest "Bacteriologic Studies of the Sputum in Patients with Chronic Bronchitis and Bronchiectasis," which appeared in the March, 1960, issue of the AMERICAN REVIEW OF RESPIRATORY DISEASES. Unfortunately, this and many other recently published studies employ cultures of expectorations to determine the flora of the lower respiratory tract.

Some time ago we studied the bacteriology of various chronic pulmonary diseases, comparing methods of collecting specimens.[1] Although we invariably found numerous pyogenic organisms in the expectorations, we rarely recovered them from the peripheral bronchi or lung at thoracotomy. We concluded that expectorations and secretions obtained at bronchoscopy were too extensively contaminated by organisms normally present in the mouth to reflect the condition of the lower respiratory tract. Since that time we have examined numerous samples of secretions obtained by tracheal puncture[2] and have obtained similar results.

In our experience, chronic infection of the lower respiratory tract with pyogenic organisms is a rare occurrence. Indeed, many acute infections of the lower respiratory tract are due to viruses and, if expectorations are relied upon for diagnosis, one may incriminate the wrong organism. It is therefore suggested that, when one wishes to determine the organism present in the lower respiratory tract, the method of tracheal puncture be employed to obtain samples of secretions.

DAVID V. PECORA
DIRAN YEGIAN
Ray Brook, New York

March 11, 1960

THE SOCIAL SCIENCES IN TUBERCULOSIS CONTROL BY CHEMOTHERAPY

To the Editor of The American Review of Respiratory Diseases:

The recommendations of the Arden House Conference on Tuberculosis[3, 4] mark an important moment in the history of the disease. In some of the latest authoritative contributions to the possibilities of chemotherapy and chemoprophylaxis as a public health measure in the fight against tuberculosis,[5, 6] the assertion has been made over and over again that the social sciences will have to play an important part in the renewed attempts for control.

Some of the questions which it is thought that the social sciences may help to answer are related to the inclusion of nonparticipating groups or individuals in diagnostic surveys, long-term control of patients under treatment, the recognition of the significant facts which regularly precede disease. In countries with general accessibility to diagnosis and treatment, low incidence of tuberculosis, high level of education, and high standard of living, like the Scandinavian countries, this last is not the least important.

I have elsewhere expressed the common opinion that the application of the social sciences to medical problems means the joint use of the main concepts and research methods used in anthropology (ethnology), sociology, and social psychology.[7] The use of any single one of these disciplines is possible but less rewarding than a joint approach; it entails more extensive theoretic limitations of the conclusions reached.

In field programs for tuberculosis control there are two critical moments in which it is necessary to give adequate consideration to the possible unfavorable reactions of the people surveyed: the first, when attempts at diagnosis are made and consist of lack of participation in diagnostic procedures or withdrawal after a diagnosis has been reached; the second, when treatment is indicated, refusal of the treatment, hesitant or inconsistent behavior, or undesirable activities (work, exertion) while under treatment.

The *cultural* elements which may be responsible for these undesirable reactions may be assumed to be the following:

(1) *Basic existential beliefs*, particularly as they concern the place of man in the universe and his fate after death. In certain cultures the hope of eternal rewards after death leads people to look upon tuberculosis and death as lesser evils or even as rewards. In others, disease is seen as a natural process which should

[1] PECORA, D. V., AND YEGIAN, D.: New Engl J Med, 1958, *258*, 71.

[2] PECORA, D. V.: J Thor Cardiov Surg, 1959, *37*, 653.

[3] National Tuberculosis Association: Bull Nat Tuberc Ass, February, 1960.

[4] U. S. Public Health Service: Public Health Rep, 1960, *75*, No. 2.

[5] World Health Organization: WHO Chron, 1959, *13*, No. 11.

[6] World Health Organization, WHO Chron, 1959, *13*, No. 4.

[7] VIJIL, C.: Public Health and Social Science, E. Munksgaard, Copenhagen, 1959.

not be interfered with, since man ought not to disturb the equilibrium of natural events.

(*2*) *Recognition of tuberculosis as a disease* is lacking in many cultures although symptoms may be interpreted as a sign of abnormality.

(*3*) *The conceptions of the causes of the disease.* It makes a great difference whether people see tuberculosis as a natural or as a supernatural event. In most cultures the concept of "infection" does not exist. The interpretation given to the facts which combine to produce disease or to cure it may vary considerably.

(*4*) *The cultural definition of methods of treatment.* When a native traditional pharmacopea exists with a model treatment for tuberculosis, the acceptance of scientific methods of treatment is unlikely.

What is important to point out is that it is possible to find individual undesirable reactions upon these same bases but in the absence of clear "cultural" premises.

It may also be pertinent to keep in mind in an effort to understand the undesirable reactions listed above the two concepts of "role" and "status" used *in sociology*, particularly in the following situations: family relationships, as sources of influences against participation and treatment; patient-physician relationships, often decisive for lack of cooperation and withdrawal; relations between staff and patients within hospitals, mobile units, clinics, and dispensaries, which are fundamental for cooperation; professional standards and norms in regard to "adequate" conduct when ill.

Possible contributions in the field of *social psychology* are: (*a*) *the design of mass propaganda campaigns* for diagnosis and treatment; the impact of the means used must be assessed and regulated; fear is altogether a bad argument; certain age cohorts are entirely recalcitrant to surveys and treatment because in the past the fear argument was too much used; the younger generations react differently: they fear the disease less; (*b*) *the study of group influence against diagnosis and treatment,* in particular at home and in the place of work; (*c*) *the need to consider each patient as an individual* with a unique personality, reactive to collective influences. Here lies the most critical area in the social sciences of today. Many theories of personality exist[8] with greatly divergent assumptions and with many contradictions. None is entirely satisfactory. The choice of a particular one implies the results obtained. The fact of personality invalidates sometimes basic assumptions of anthropology and sociology.

Whatever the hypotheses and research methods used by the social scientist in concrete cases, what is important is that he come to grips with the core of the problems raised by individual unfavorable reactions to proposals of diagnosis or treatment. They may be representative of group or partial mass reactions.

The ambulatory patient under chemotherapy ought to be under some sort of control in order to detect misuse or refusal of the drugs. He must be convinced of the necessity to take drugs regularly and consistently for two or four years. This is difficult and a highly trained personnel is needed.

The number of tuberculosis experts trained in the social sciences is very small as well as of social scientists interested in tuberculosis work. This is likely to make some recommendations of the Arden House Conference look as pious wishes.

Some experience in large trials with chemotherapy is already available in several countries. It needs to be collected and codified for general information.

In Sweden, the number of unfavorable mental reactions with isoniazid, particularly in young people, seems to exclude large prophylactic and therapeutic trials, were they thought to be necessary.[9]

In summary, the social sciences may certainly contribute to the future nation-wide efforts for tuberculosis control advised by the Arden House conference. The concepts and research methods used in anthropology, sociology, and social psychology ought to be used jointly. A schema has been provided of a few areas in which research may be rewarding. There are important theoretic and practical limitations to the use of the social sciences; but, if the problems are the same as they were forty years ago, we can see them now under a more operational aspect. What is needed is more research.

C. Vijil
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April 18, 1960

CHEMOTHERAPY TO PREVENT RELAPSE IN NONINFECTIOUS TUBERCULOSIS

To the Editor of the American Review of Respiratory Diseases:

In July, 1959, you published a letter from Dr. W. H. Oatway, Jr., on the subject of chemotherapy to prevent relapse in patients with noninfectious tuberculosis. One of the three groups for which he suggested chemotherapy were patients who had once had clinical tuberculosis but whose

[8] Hall, C. S., and Lindzey, G.: Theories of Personality. Wiley and Sons, New York. 1957.

[9] Birath, G.: Personal communication, 1960.

disease was now inactive, and who had never had chemotherapy.

We have recently completed a pilot survey of chemotherapy for roentgenographically stable tuberculous lesions among patients who had never previously received chemotherapy. Fifty-five patients were included in the survey; all had pulmonary shadows which were assumed to be of tuberculous origin and were considered not to have changed for at least three years. None had clinical or bacteriologic evidence of activity, as judged by the history, symptoms, weight, clinical examination, and laryngeal swab cultures taken over the previous three years. They were assessed at the beginning and end of a one-year period by postero-anterior chest films and tomograms.

During this year, 27 patients were treated with calcium benzoyl PAS in a total daily dose of 10.5 to 12 gm., and isoniazid, 230 to 300 mg. Of the 27 treated patients, 3 improved roentgenographically and none deteriorated. One of the 28 untreated patients deteriorated during the year; and a second deteriorated four weeks afterward.

These findings would support your contributor's contention that such patients might well be given a year's chemotherapy in an attempt to prevent relapse. The numbers are, however, small, and the investigation of a larger series would be well worth while. We propose to follow our patients for a further five years.

ZAIDA M. HALL
PHILLIP A. ZORAB
KEITH E. JEFFERSON
Paddington & Kensington Chest Clinic
London, W. 2, England

April 25, 1960

Books

CURRENT THERAPY—1959: Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn. Pp. 781, W. B. Saunders Company, Philadelphia, and London, 1959. Price, $12.00.

This volume is designed to bring "to the practicing physician current and authoritative therapeutic procedures in concise and specific terms designed for ready application to the problem at hand." Most of the twelve consulting editors are recognized internationally as authorities in their respective sub-specialties.

The participants should have a sense of satisfaction in their effort because there have been improvements made over previous editions. Emphasis is placed on the management of illness. Only brief résumés have been made of the natural history and complications of the various disease states. The methods of treatment advocated are generally recognized and supported by available objective information. However, additional improvements should be made, in the reviewer's opinion. For example, in streptococcal infections, the testing of Group A streptococci susceptibilities to antimicrobials is not necessary because the vast numbers of isolates in this group are markedly susceptible to penicillin, et cetera. Elsewhere, the attempt to distinguish between the several tetracyclines and their several salts and adjuvants is of no practical significance because of the similarities of the clinical and pharmacologic features of these preparations.

The book includes a table of laboratory values indicating the normal values in adults and in children, a table of pediatric dosage of many medications currently widely employed, and a listing of the drugs suggested by the individual writers for use in the many disease states covered in the book. The reviewer accepts as inevitable the current wide use of proprietary names for drugs, as employed in the roster of drugs in this volume. However, it is suggested that the addition of the chemical or generic name of the active substances in parentheses following the proprietary name would provide information useful to the practicing physician. The latter practice has been followed in the tables of poisonous substances commonly encountered, which form a large section.

Proof of the usefulness of this book is in the sale of over a quarter of a million copies in its successive editions, according to the publisher. In the reviewer's opinion, the attempt to combine current treatment in medicine and in surgery into one volume, although commendable, still falls short of the standards established by selected current editions of textbooks of medicine and surgery.

CARL A. BERNTSEN, JR.
449 East 68th Street
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DIE TUBERKULOSE IHRE ERKENNUNG UND BEHANDLUNG. By Hellmuth Deist and Hermann Kraus. Pp. 847, Ferdinand Enke Verlag, Stuttgart, Germany, 1959. Price, DM 138.

If one defines the purpose of a textbook to be to introduce the professional reader into a given field of medicine with the aim to procure for him a secure base from which he may practice his specialty, the work under review has certainly fulfilled it. The editors, two outstanding German physiologists, certainly deserve praise for the skill with which they have chosen their contributors and succeeded in the limited space of eight hundred pages to provide a complete picture of our present knowledge of the disease, tuberculosis.

As a rule, every book which has been compiled by a number of authors contains one outstanding contribution. There is no doubt in the reviewer's mind that in the present instance this place belongs to Dr. Knapp's article on the immunology and bacteriology of tuberculosis, which represents perhaps the most brilliant contribution in this particular field in the past few years. Dr. Letterer's article on the general pathology of tuberculosis summarizes the vast experience gained not only from his own investigations but also from that of other well-known pathologists such as Hübschmann and Wurm. It is interesting to note that Dr. Letterer conceives the sepsis acutissima as an expression of hyperergy; miliary chronic disseminating tuberculosis, on the other hand, as expressions of relative immunity.

As one would expect from a book of this scope, every clinical manifestation of tuberculosis has been discussed in greatest detail. Thus, the article by Dr. Deist gives a very well-written introduction into diagnosis and treatment of pulmonary tuberculosis, which is made even more interesting by a discussion of typical clinical cases taken from the author's vast experience. A few errors have slipped into the chapter on differential diagnosis: coccidioidomycosis is not endemic in South Carolina, but in California. Furthermore, North

American blastomycosis, South American blastomycosis, and the European blastomycosis (as described by Busse and Buschke in Berlin in 1892) do not only represent clearly different disease entities, but also are caused by entirely unrelated organisms and should therefore be kept separate.

Dr. Breu's chapter on the medico-legal aspects of the disease might in many respects be of interest to the American public health officer, particularly with regard to the question under which circumstances the German government recognizes tuberculous infection as a consequence of military service.

In studying Dr. Kraus' article on the surgical methods of treatment, the impression is received that the European viewpoints in this matter are not any longer fundamentally different from the American ones. Indications for operative intervention and operative methods are largely in agreement with those discussed and suggested at the U. S. Veterans Administration-Armed Forces conferences. The same may be said with respect to the very lucid and comprehensive contributions by Professors May and Kraus and Dr. Hutschenreuther on tuberculosis of the skeleton and the abdomen, respectively. The illustrations which accompany these articles are without exception well-chosen, representative and, from the viewpoint of reproduction, excellent.

Dr. Simon, who first described the "Spitzentuberkulose," certainly requires no introduction. From his pen stems the highly interesting chapter on childhood tuberculosis. In the general review of the problem, the possibilities of superinfection are stressed. In the special, clinical part, emphasis is placed on the occurrence of rupture of caseous lymph nodes into the bronchial tree.

Although tuberculosis of the female genitals has decreased in significance since the war, it still offers a significant problem in Germany, as Dr. Winkler points out in his article on this subject. The most frequent form is, in his experience, tuberculous salpingitis which reaches a peak between the twenty-fifth and thirtieth years of life. With conservative treatment, clinical cure can be effected in about 70 per cent of the cases. Pregnancy as such is not necessarily associated with a worsening of the patient's status, but both induced and spontaneous abortion may have disastrous consequences.

The chapter by Professors May and Dr. Schultze-Seemann on tuberculosis of the urogenital tract stresses the close relationship of renal prostatic and testicular tuberculosis. For early diagnosis of renal processes, the authors recommend a certain modification of the intravenous pyelogram, and point out that this method in their hands has proved superior to the retrograde pyelogram. They hold the opinion that excretion of tubercle bacilli is invariably associated with tuberculous disease of the kidney, which appears debatable in the light of recent evidence. As a whole, a conservative therapeutic approach is recommended.

The contribution on tuberculosis of the skin is written by the well-known German dermatologist, Professor Gottron, who presents his subject in a most engaging and interesting manner. Both histologic descriptions and illustrations are chosen with great care and make the reading of the chapter most agreeable. The author dwells on the histology of erythema nodosum, and emphasizes that endangitis is a rarely missing characteristic. The difference between miliary tuberculosis of the skin and disseminated lupus is seen in the formation of typically necrotic foci in the first, and appearance of tubercles in the second case. Stress is placed on the demonstrability of tubercle bacilli in the tuberculid skin lesions. Two minor errors are noted: the formula of isoniazid on page 722 is misprinted, and the statement that the peak of tuberculosis mortality lies between the thirtieth and fortieth years of life stands in contrast to all available statistical evidence.

A brief but very lucid chapter on tuberculosis of the eye has been contributed by Professors Stock and Sautter. They emphasize the rare occurrence of retinal tuberculosis, and take issue with the widely held view that chronic uveitis is chiefly caused by tuberculous infection.

The last three articles on tuberculosis of the ear, pharynx, and large bronchi have all been contributed by Professor Arold. The author holds that modern chemotherapy has proved particularly beneficial in this field and has made a more conservative approach possible.

This book without doubt fills a gap in the German medical literature and provides an invaluable source of information for the phthisiologist. Because of the carefully selected, up-to-date bibliographies, and the high quality of its illustrations, it should prove of definite value also to the American specialist with sufficient command of the German language.

DIETHELM BÖHME
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ANTIBIOTICS ANNUAL, 1958–1959. Edited by Henry Welch and Felix Marti-Ibanez. Pp. 1106, Medical Encyclopedia, Inc., New York, 1959. Price, $12.00.

This annual compendium, like its predecessors, is a useful and at times very interesting book.

Clinical reports on the effectiveness of the newer antimicrobial agents are gathered in sections, providing the reader with a reasonable picture of the available clinical information about specific newer drugs. Some of these reports, however, lack the controls and precise observations that are present in others.

There is some very precise information presented about some of the drugs discussed regarding dosage, blood levels, rates of excretion, effectiveness, and toxicity related to dosage and route of administration. This information is invaluable for the clinician faced with a resistant infection in which a new form of therapy is contemplated.

One shortcoming of this type of review is that it does not include any information regarding the mode of action of the drugs discussed, nor an appraisal of the very close relationship that some of them have to each other.

Perhaps one of the most interesting sections in the book is at the very beginning, in which a past, present, and future perspective of the development and consequences of antimicrobial therapy is presented. This section includes remarks made by such highly regarded people as Sir Howard Florey, Dr. Waksman, Dr. Keefer, and Dr. Dowling.

Jerome L. Schulman
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A Clinical Introduction to Heart Disease. By Crighton Bramwell. Pp. 229, Oxford University Press, New York, 1959. Price, $5.50.

This is an unusual book on elementary cardiology. It is necessary to state at once that it is not written for specialist physicians, let alone for cardiologists, but for general practitioners and for students aiming for general practice. For them it represents a refreshing and highly personal account of the basic principles of cardiology. Dr. Bramwell has deliberately avoided more than a mention of procedures suitable only for hospital use, and has avoided also all mention of rarities. He has concentrated on looking back over his own experience and describing the details of clinical diagnosis and the methods of treatment which are most applicable in the patient's home. Thus, the greater part of his book is concerned with general problems of diagnosis and treatment, heart failure, myocardial ischemia, and disorders of rhythm, with little said about the specific etiologic types of heart disease. The author has tried to correlate the clinical descriptions with their physiologic background, and has been led into perhaps undue detail in certain fields, such as analysis of the pulse wave, in which he has himself contributed to our knowledge.

By contrast, he has perhaps paid too little attention to another of his special interests, the problem of heart disease and pregnancy, and it would have been interesting to have read numerical details of his own extensive studies of this subject.

Certain details invite criticism. For example, no mention is made of the use of steroids in treating acute rheumatic fever; and few would now recommend calomel in the treatment of hypertension. Again, the author places great emphasis on the actual level of the blood pressure in the assessment of hypertension, whereas most physicians would feel that evidence of vascular damage is of greater prognostic importance than the casual blood pressure reading.

The author has largely succeeded in his aims, and his book will be read by practitioners with enjoyment and profit.

Harold P. Lambert
University College Hospital
London, England

BOOKS RECEIVED

The Practice of Medicine (Sixth Edition). Edited by Jonathan Campbell Meakins. Pp. 1916, The C. V. Mosby Company, St. Louis, Missouri, 1956. Price, $16.00.

Histoplasmosis. Edited by Henry C. Sweany. Pp. 538, Charles C Thomas, Springfield, Illinois, 1960. Price, $14.50.

Antibiotics Annual 1959–1960. Edited by Felix Marti-Ibañez. Pp. 1034, Antibiotica, Inc., New York, 1960. Price, $15.00.

Heritable Disorders of Connective Tissue (Second Edition). By Victor A. McKusick. Pp. 333, The C. V. Mosby Company, St. Louis, Missouri, 1960. Price, $12.00.

Virus Virulence and Pathology. Ciba Foundation Study Group No. 4. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Pp. 114, Little, Brown and Company, Boston, 1960. Price, $2.50.

Obituary

Ralph Horton
1901–1959

Dr. Ralph Horton, the son of a physician and the father of a medical student, was born in Jane, Missouri, on January 13, 1901. He earned his A.B. at the University of Missouri (1924) and his M.D. at the University of Kansas (1926). Immediately commissioned as assistant surgeon in the U. S. Public Health Service, he served as intern, resident, and staff member at their hospitals in New Orleans, Baltimore, Detroit, and New York City until 1929. After a brief period of private practice in Dexter, Missouri, he was found to have pulmonary tuberculosis. Convalescing quickly, he joined the staff at Loomis Sanatorium, Liberty, New York (1930–1932). Motivated by his interest in public health and tuberculosis, he joined the New York State Department of Health, Tuberculosis Control Division, in 1932, an association which continued throughout his life. Early in this phase of his career he demonstrated superior natural talent for leadership and organization. As a result, he was made the first Director (1934) of the then-new Homer Folks Tuberculosis Hospital at Oneonta, New York, an appointment which gave him a full personal and professional life.

In his community he was held in high esteem and affection because of his work in numerous activities which made Oneonta a better place in which to live. On a national scale he was an industrious member of the American Trudeau (now Thoracic) Society, the National Tuberculosis Association, the American Public Health Association, and the American College of Physicians. Especially in the first two of these societies, he served on many important committees, often as chairman. His chief interests here related to establishment of both standards of hospital construction and organization and criteria leading to progressively better quality of patient care. He was largely responsible for the 1950 edition of the *Diagnostic Standards* of the National Tuberculosis Association. In spite of the demands upon the administrative and medical head of a tuberculosis hospital, he found time to contribute numerous valuable articles to the medical literature as well as teaching medical students.

If Ralph had been simply a physician, he would have merited high praise because he was great in his chosen field of pulmonary disease. He brought to medicine the skill of the accomplished healer but, even more, the sensitivity and devotion of a lover of humanity.

He died as he might have wished, at the end of a busy day of labor for others, on September 18, 1959. He is survived by his wife, Laura Catlin Horton, his son William, and his daughter Nancy.

N. Stanley Lincoln

NOTICES

The following dates and locations of the next four annual meetings of the National Tuberculosis Association and the American Thoracic Society have been selected and approved:

1961—Cincinnati, Ohio—May 21–26
1962—Miami Beach, Florida—May 20–25
1963—Denver, Colorado—May 12–17
1964—New York, New York—May 24–29

1961 ANNUAL MEETING OF THE AMERICAN THORACIC SOCIETY

INVITATION

The Medical Sessions Committee *INVITES SUBMISSION OF PAPERS* on all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary diseases for presentation at the *1961 ANNUAL MEETING IN CINCINNATI, OHIO, MAY 22–24.*

ABSTRACTS

(*1*) Abstracts of papers to be offered for presentation should be submitted before January 7, 1961 to the Chairman of the Medical Sessions Committee. *EIGHT COPIES* are required for distribution to committee members.

(*2*) Abstracts should be limited to a 300-word summary including *IMPORTANT DATA AND CONCLUSIONS.* Charts and tables should be attached to aid in the selection of papers. Abstracts selected for presentation at the Annual Meeting will be published in THE AMERICAN REVIEW OF RESPIRATORY DISEASES.

(*3*) Reports of interesting or unusual cases will be considered for inclusion in case conferences.

(*4*) The names, academic degrees, titles, and complete addresses of the senior author and co-authors should be included in each abstract.

(*5*) All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation.

(*6*) Authors will be notified by February 20, 1961, if their papers have been accepted for presentation.

(*7*) Papers presented at the Annual Meeting must be *ORIGINAL* contributions *NOT PREVIOUSLY PRESENTED OR PUBLISHED.* Medical papers presented at the meeting may be submitted to THE AMERICAN REVIEW OF RESPIRATORY DISEASES by the author if he so desires.

SUGGESTIONS

The Medical Sessions Committee is particularly anxious to build the 1961 program around your special interests. A memorandum suggesting subjects and speakers would be welcome and should be sent to the Chairman by September 20, 1960.

L. H. Schmidt, Ph.D., *Chairman*
Medical Sessions Committee
American Thoracic Society
1790 Broadway, New York 19, N. Y.

NATIONAL TUBERCULOSIS ASSOCIATION FELLOWSHIPS

As the Medical Section of the National Tuberculosis Association, the American Thoracic Society (formerly the American Trudeau Society) provides fellowships and traineeships for the graduate education of investigators and teachers in the field of respiratory diseases and tuberculosis. The following types are offered:

Edward Livingston Trudeau Fellowships: A few fellowships at a higher level of training and award are offered to specially qualified candidates with an M.D. degree who have been assured of a continued teaching or research appointment upon completion of training. Trudeau Fellowships are awarded for one year, but may be renewed up to a total period of four years.

Research Fellowships: Postdoctoral fellowships are offered to candidates holding the degree of M.D., Ph.D., or Sc.D. for further training as scientific investigators.

Predoctoral fellowships are offered to graduate students with a bachelor's degree to work on a research project for an advanced degree other than M.D.

Teaching Traineeships: Physicians entering their second or third year of residency in Internal Medicine or Thoracic Surgery at a medical center who may be interested in a career of medical teaching are offered traineeships toward that end. Supplementation of these awards by the institution involved is not necessary.

Each applicant for an NTA fellowship or traineeship must have been accepted by the head of the department under whom he expects to work for the next academic year in this country. Awards are determined by individual circumstances and are paid directly to the Fellow on a quarterly basis. They are granted for one year, beginning on any date after April first, and are renewable for a total of three years.

All applications must be submitted by November 1st. Further information about Fellowships may be obtained upon request from:

Director of Medical Education
American Thoracic Society
1790 Broadway
New York 19, New York

LABORATORY REFRESHER TRAINING COURSES

The following schedule of Laboratory Refresher Training Courses is being offered by the Laboratory Branch of the Communicable Disease Center from October 10, 1960, to April 7, 1961. Information and application forms may be obtained from the Laboratory Branch, Communicable Disease Center, U. S. Public Health Service, Atlanta 22, Georgia.

Schedule of Laboratory Refresher Training Courses
July, 1960—June, 1961

Dates	Courses	Duration (*weeks*)
October 10–21	Fundamentals of Virology (819)	2
October 31–November 11	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2
November 28–December 2	Laboratory Methods in the Diagnosis of Rabies (826)	1
December 5–9	Bacteriophage Typing of Staphylococci (856)	1
January 9–February 3	Laboratory Methods in Medical Mycology (815)	4
January 23–February 10	Serologic Methods in Microbiology (941)	3
January 30–February 10	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2
February 13–24	Laboratory Methods in the Study of Pulmonary Mycoses (817)	2
February 27–March 17	Laboratory Methods in Medical Bacteriology (838)	3
March 6–10	Laboratory Diagnostic Methods in Veterinary Mycology (940)	1
March 13–31	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases (820)	3
March 20–24	Special Problems in Medical Bacteriology (839)	1
March 27–April 7	Laboratory Methods in Enteric Bacteriology (850)	2
April 3–7	Laboratory Methods in the Diagnosis of Rabies (826)	1
*	Laboratory Methods in the Diagnosis of Malaria (805)	1
*	Special Training in Virus Techniques (821)	2–4
*	Typing of *Corynebacterium Diphtheriae* (842)	1
*	Special Problems in Enteric Bacteriology (851)	2
*	Phage Typing of *Salmonella Typhosa* (852)	1
*	Laboratory Methods in the Diagnosis of Leptospirosis (853)	1–4
*	Serologic Differentiation of Streptococci (854)	2
*	Special Problems in Microbiology (942)	1–2

* Courses given by special arrangement only.

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

ABSTRACTS

Edited by EDWIN D. KILBOURNE
Editorial Assistant: TERRI MANN

VOLUME 82 August 1960 ABST. NO. 2

The Editor recognizes the inevitable incompleteness and arbitrary selectivity of any abstracting service, including this one. It is his belief that the usefulness of the present Abstracts section will be enhanced if the reader is informed of the general purpose of the abstracts and the criteria employed in their selection.

It is the purpose of the Abstracts section to acquaint the diversified and international readership of the REVIEW with the gist of original and scientific articles which are related to the general subjects of tuberculosis or respiratory diseases implicit in the title of the journal. In this connection, 42 abstracters systematically review 239 journals which represent 36 countries and which are published in 22 languages. In most instances, abstracters cover journals in fields of their special competence. It is evident that the diverse interests of the readers of the REVIEW dictate a balanced selection of clinical, laboratory, and epidemiologic studies. Such selection will often preclude the publication of articles equal in scientific merit to many presented here.

In the publication of abstracts, cognizance is taken of the extent to which the journals yielding them are circulated. Articles from journals of wide circulation may be mentioned by title only. This space-saving device is also employed for articles which defy condensation without the omission of essential data or discussion. The attention of readers is thus directed to the existence of papers which are no less important because they are not summarized.

(Requests for further information on abstracted articles should be directed to the author of the article at the address indicated by an asterisk (*) in each abstract title.)

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NONTUBERCULOUS THORACO-PULMONARY DISEASE

The Coming Winter. Leading Article. *Tubercle*, October, 1959, 40: 389–390.

Some years ago, when chest physicians were mainly concerned with pulmonary tuberculosis, the changing seasons caused relatively little alteration in the volume of their work and no particular preparation was required against the exigencies of winter. The altered situation with regard to tuberculosis has brought about considerable change; few chest hospitals and fewer clinics are insulated now against the seasonal variations in respiratory disease, and winter in Britain means more work for the chest physician. It is anticipated that, some time after Christmas, demands for beds in many areas will outrun the available supply; and if this should happen to be a bad year for influenza, the situation will be proportionately worse. Fog and flu in February rendered last winter unduly severe, but there is some reason to believe that a bad winter in regard to bronchitis mortality is usually succeeded by one of lesser severity; perhaps the susceptible are killed off in larger numbers in the more disastrous years, leaving a lesser harvest for the ensuing winter. But there is little indication that deaths from bronchitis are tending to decline, and the pool of potential victims seems to be constantly replenished. Modern therapy, successful with pneumonia and tuberculosis, has so far signally failed to produce similar results with bronchitis, and each winter brings a flood of admissions.

"Bronchitis" in its early stages gives no clear-cut picture, and often the symptoms are so intermittent and the deterioration so gradual that damage of an irrevocable nature is present before effective action can be taken. It would seem that we must set our diagnostic sights considerably higher and regard cough and sputum lasting for more than a month as an indication, not only for a chest roentgenogram, but for a thorough assessment of the chest condition. In the past we have never been disconcerted by the large percentage of "normals" who have been roentgenographed to exclude tuberculosis; in this new field the presence of persistent cough and sputum, not due to bronchiectasis, sinusitis, lung cancer, or other apparent cause, should be regarded as indicative of bronchitis until proved otherwise; nor can a normal film be regarded as necessarily indicating a healthy bronchial tree. At this early stage of the condition, hospital admission will seldom be necessary. Recurring chest infections can be promptly and adequately treated and the patient can, if he has wise advice and a strong will, stop smoking cigarettes. But it is seldom possible for him to change his environment. He must live where there is work to be had; and where there are large concentrations of industry and people in Great Britain there is also polluted air. We cannot change our climate; but we can clean our air if we make sufficient effort. The progress made so far is pitifully small.
—M. J. Small

The Bronchi in Older Persons (in Italian). A. Ferraris*. *G Ital Tuberc*, March–April, 1959, 13: 63–71. (*Cl. Tisiologica, U. of Genoa, Italy)

The results of this study are based upon the bronchoscopic and bronchographic observations of 320 persons older than 55 years. The following pathologic alterations were found (no percentages are given): (*a*) atrophic, hypertrophic, and bronchorrhagic bronchopathy, or mixed forms; (*b*) deviation of the trachea and bronchi due to fibrotic processes; (*c*) compression caused by adenopathy; (*d*) bronchial malacia, frequently symptomatic and restricted to the distal portion of the trachea and to the proximal part of the large bronchi, rarely diffused, and of the "essential" type; (*e*) deforming bronchitis; (*f*) bronchiectasia, rather rare in the more obvious form, frequent in the rosary-bead form in association with atrophic and deforming bronchitis. In addition, functional alterations of motility, susceptibility to cough, drainage and expulsion of secretions, and increase and qualitative variations of the secretions were observed.—I. Archetti

Spontaneous Pneumothorax Complicating Bronchial Carcinoma. K. M. Citron*. *Tubercle*, October, 1959, 40: 384–386. (*Brompton Hosp., London, England)

Three patients with primary bronchial carcinoma presenting with spontaneous pneumothorax, and another 3 patients with known or suspected bronchial carcinoma who had spontaneous pneumothorax during the course of their disease are described. The spontaneous pneumothoraces in these patients did not have the features usually associated with malignant disease, because expansion of the lung was usually spontaneous and complete and occurred without the formation of any appreciable quantity of pleural effusion. The most likely explanation of the pneumothoraces in the patients described here would seem to be that the bronchial carcinoma caused pleural rupture indirectly. Thus, compensatory overexpansion of part of a lung associated with lobar or segmental collapse due to a neoplasm might have caused rupture of a bulla in the overexpanded portion of lung.

While primary bronchial carcinoma is rarely complicated by spontaneous pneumothorax, the present high frequency of bronchial carcinoma

makes it desirable to consider this in the diagnosis of the cause of certain cases of spontaneous pneumothorax. Abnormal roentgenographic shadows are often seen in the lung when partly collapsed by a pneumothorax. These shadows usually clear when the lung is expanded. Persistent shadowing after expansion or during delayed expansion of the lung should suggest carcinoma of the bronchus, and is an indication for bronchoscopy.—M. J. SMALL

Needle Biopsy of the Parietal Pleura in Malignant Disease. P. O. LEGGAT*. *Brit Med J*, September 19, 1959, No. 5150: 478–479. (*Newcastle Regional Hosp. Board, England)

Twenty-two parietal pleural biopsies were performed in 30 cases of pleural effusion associated with malignant disease. The Abrams needle proved more satisfactory than the Vim-Silverman needle. In 12 cases (60 per cent) the diagnosis was confirmed, in 7 (35 per cent) nonspecific fibrous tissue was obtained, and in 1 case the specimen was inadequate. Malignant cells were demonstrated in 8 cases (40 per cent) when the pleural fluid was examined. In 6 (30 per cent) of the cases the only means of diagnosis was needle biopsy, while in a further 6 (30 per cent) it was confirmatory.—E. A. RILEY

Chronic Idiopathic Pericardial Effusion without Tamponade. D. C. CONNOLLY*, T. J. DRY, C. A. GOOD, O. T. CLAGETT, and H. R. BURCHELL. *Circulation*, December, 1959, 20: 1095–1105. (*Mayo Clinic, Rochester, Minn.)

Persistent pericardial effusion in the absence of obvious preceding or concurrent disease presents a baffling problem. In such cases, chylopericardium, cholesterol pericarditis, lupus erythematosus, malignant disease, myxedema, severe anemia, and scleroderma must be considered. Six cases are reported with gross effusions of unknown cause, present from 1 to 11 years without the development of cardiac tamponade. The diagnostic measures used, the inconclusive results of histologic examination, and the effects of surgery on the clinical course are discussed.
—W. J. STEININGER

Clinical Evaluation of Radioactive Chrome Phosphate in the Control of Malignant Pleural and Ascitic Effusions. C. R. PERRYMAN*, E. J. PAVSEK, and J. D. MCALLISTER. *Radiology*, December, 1959, 73: 865–870. (*Mercy Hosp., Pittsburgh, Penn.)

In the treatment of malignant effusions, radioactive chrome phosphate is deemed the agent of choice in preference to colloidal gold and radioytrium. In a series of 60 cases in which radioactive chrome phosphate was used in doses of 5 millicuries, results were better in control of pleural than of peritoneal fluid. Excellent results were obtained in 12 of 38 malignant pleural effusions, and in only 4 of 22 ascitic effusions. It is now believed that a dose of 10 millicuries should be used in the abdomen, and 5 to 8 millicuries in the chest. Radioactive chrome phosphate is preferred to nitrogen mustard because of the latter's generalized cytotoxic effect. Triethylenethiophosphoramide (Thio-TEPA®), one of the newer nitrogen mustard compounds, merits investigation.—W. J. STEININGER

Electrocardiographic Studies in Pulmonary Disease. D. H. SPODICK*. *Circulation*, December, 1959, 20. (*Lemuel Shattuck Hosp., Boston, Mass.)

I. Electrocardiographic Abnormalities in Diffuse Lung Disease: pp. 1067–1072:

Analysis of the electrocardiograms of 79 consecutively admitted patients with diffuse lung diseases suggests a marked and relatively specific effect of diffuse lung disease upon both normal and abnormal electrocardiograms. Verticalization of the mean frontal P-axis is the most constant single characteristic. Other factors occur in most cases, but are frequently absent. Among these are Gothic and pulmonale-type P-waves, vertical QRS axis, deep S-waves over the left precordium, and prominent diphasic P-waves over the right precordium. Absence of rightward frontal P axis is strongly against the presence of diffuse lung disease, but absence of any other single factor is of little statistical value in itself.

II. Establishment of Criteria for the Electrocardiographic Inference of Diffuse Lung Disease: pp. 1073–1078:

Criteria based on frontal P-wave axis and configuration which are proposed for the electrocardiographic detection of diffuse lung disease proved highly accurate in a "blind" evaluation of 100 consecutively admitted patients without cardiac arrhythmias. Diffuse lung disease was positively identified in 93 per cent or excluded in 96 per cent of the cases, with the exception of a small "possible" group (10 per cent of patients in this series) in whom the accuracy was only 60 per cent. If the "possible" group is included with the "positive" group, 86 per cent were correctly diagnosed, 6 per cent were falsely labeled. It is proposed that the criteria described are adequate for a new standard electrocardiographic interpretation: "consistent with diffuse lung disease."
—W. J. STEININGER

Long History of Heavy Smoking as a Factor Causing Obstructive Pulmonary Emphysema. K. A. J. JARVINEN* and K. THOMANDER. *Ann Med Intern Fenn*, Fasc. 4, 1959, 48: 211–217. (*U. of Helsinki, Finland)

The incidence of chronic smoking and certain other factors causing chronic bronchiolar irritation was examined in 2 carefully selected groups. One consisted of 42 cases of diffuse obstructive pulmonary emphysema (OPE), the other of 50 persons with healthy lungs. Besides the similarity in the method of selection, the groups corresponded mutually in age and sex distribution. Chronic heavy smokers (minimum of 15 gm. of tobacco per day, regular smoking for not less than 10 years) in the OPE group totaled 36, and in the control group, 19. Of 11 women with OPE, 6 were heavy smokers, while 1 woman of 17 with healthy lungs was a heavy smoker. Thirty-five of the 42 subjects in the OPE group had chronic bronchitis. Not a single subject in the control group had chronic bronchitis. In the OPE group, 7 subjects had histories of bronchial asthma for 10–46 years, and 2 had fairly severe asbestosis. OPE is known to originate as the result of chronic bronchiolar irritation and accompanying bronchiolar obstruction. Indeed, all of the factors causing bronchiolar irritation merit attention. Recurrent infections of the respiratory system have been thought to play a fairly important part in this sense in the etiology of OPE. Of the other factors associated with the etiology of OPE and considered in the present investigation, chronic smoking came first, bronchial asthma second, and pneumoconiosis third (after authors' summary).—E. DUNNER

Association of Cardiac Pulmonary Haemosiderosis and Fibrosis. P. ELLMAN* and R. A. M. OLIVER. *Brit Med J*, November 14, 1959, No. 5158: 988–991. (*St. Stephen's Hosp., London, England)

Two cases are described of pulmonary hemosiderosis associated with recurrent hemoptysis due to mitral stenosis. In the first case, the miliary lesions, which cleared after successful valvotomy, are described. In neither case was any significant degree of pulmonary fibrosis present.
—E. A. RILEY

Idiopathic Pulmonary Hemosiderosis (in Slovak). L. IVIČIČ and J. KRAJÁK*. *Lek Obzor*, December, 1958, 7: 732–738. (*Komensky U., Košice, Czechoslovakia)

The authors describe a case of idiopathic pulmonary hemosiderosis in a 4-year-old girl. The diagnosis was confirmed in the laboratory by the finding of macrophages containing hemosiderin in the tracheal mucus. Splenectomy was performed, but no improvement followed.
—J. ILAVSKY

Hypoplasia of the Lung: Report of a Case (in Japanese). H. YAMASHITA*, T. NAKANO, M. ASAI, Y. MATSUDA, and T. MIKAMI. *Clin Radiol*, January, 1960, 5: 64–69. (*Fujimi Hosp., Shizuoka Prefecture, Japan)

A 12-year-old underdeveloped girl presented a diagnostic problem because her roentgenogram showed cloudiness of the left hemithorax except in the small areas of the upper and lower medial portions. Serial planigrams and bronchography revealed that the right bronchi were abnormally well developed, the right upper and medial portion of the middle lobe extended into the left hemithorax, the left lung was hypoplastic, and only the S_{10} segment functioned in the left lower medial lung field. The heart was completely displaced in the left hemithorax, and the maximal apical impulses were palpable in the fifth intercostal space on the anterior axillary line. The roentgenogram of this patient was initially interpreted as indicating adhesive pleurisy? Differential diagnostic problems from mediastinal hernia, atelectasis, et cetera, are discussed.—I. TATENO

North American Blastomycosis. G. L. BAUM* and J. SCHWARZ. *Amer J Med Sci*, December, 1959, 238: 661–684. (*Jewish Hosp., Cincinnati, O.)

In North America, blastomycosis should be suspected in all chronic pulmonary disorders of granulomatous character which are not tuberculous, histoplasmal, or of other mycotic origin. Even when tumor is suspected from roentgenograms, blastomycosis should not be ruled out. The clinical manifestations of the disease are those of an indolent infection which is primary in the lung and which disseminates to all organs, but predominantly to the skin. The ultimate prognosis in the untreated case depends on the activity of the pulmonary focus. There is no proof of transmission from man to man or animal to man. Problems which await solution include the peculiar geographic distribution of the disease and the natural source of the organism *Blastomyces dermatitidis*. North American blastomycosis is an almost conquered disease. The excellent response to amphotericin B and, in many cases, to stilbamidine and its derivatives has removed the fear of the diagnosis. Clinical awareness and search for the organism will obviate mistakes in diagnosis and lead to effective therapy.—W. J. STEININGER

Clinical Manifestations of Pulmonary Blastomycosis. R. ABERNATHY*. *Ann Intern Med*, October, 1959, 51: 707–727. (U. of Arkansas, Fayetteville)

A series of 35 patients with blastomycosis has been reviewed. Disseminated lesions occurred in 28 patients, 3 exhibited cutaneous lesions only, and 4 had only pulmonary blastomycosis. Since pulmonary involvement was found in 27 cases, particular analysis was made of the clinical manifestations of pulmonary blastomycosis. Symptoms included cough, sputum, fever, chills, hemoptysis, significant dyspnea, and pleuritis. Physical findings were not impressive; however, free pleural effusions and pneumothorax were seen. Roentgenographic features similarly were not specific; the pattern found most frequently was one showing an infiltrative or fibrotic reaction, with pleural reactions and thoracic adenopathy occurring often. Infrequent patterns included cavities, miliary lesions, pneumonia, and an appearance suggestive of bronchogenic carcinoma.

No specifically diagnostic clinical pattern could be established for pulmonary blastomycosis. The occurrence of parenchymal pulmonary disease, in association with cutaneous, pleural, bone, or thoracic nodal involvement, should strongly suggest the possibility of blastomycosis. However, because of the extremely varied clinical manifestations of pulmonary blastomycosis, this diagnosis should be considered in any pulmonary disease of undetermined origin (Author's summary). —T. H. NOEHREN

Primary Clostridial Pneumonia. J. SWEETING* and L. ROSENBERG. *Ann Intern Med*, October, 1959, 51: 805–810. (*National Institutes of Health, Bethesda, Md.)

A case is presented of a primary pneumonia with lung abscess formation due to *Clostridium perfringens* (*Bacillus welchii*). A 45-year-old white housewife was admitted with the complaints of dyspnea and ankle swelling of 7 to 10 days' duration. The illness had begun 3 to 4 weeks prior to admission, when she had experienced 3 or 4 days of headache, backache, and a "feverish feeling," without cough, nausea, vomiting, diarrhea, or chills. The original symptoms subsided in 72 hours without treatment, but she continued to feel weak, tired, and breathless on slight exertion. Ten days before admission she noted severe dyspnea on climbing 2 flights of stairs, and approximately 1 week later she complained of swelling of her feet and ankles, as well as dyspnea. Within 48 hours the swelling involved her entire lower extremities, and she therefore sought admission.

Physical examination revealed a critically ill white woman with obvious jaundice, cyanosis, and tachypnea. Pulse, 150 per minute; respirations, 30 per minute and shallow; blood pressure, 180/110 mm. Hg. in both arms; temperature, 102.6°F. The sclerae were icteric, but no spider angiomas or other skin lesions were noted. Neck veins were distended and filled from below. Examination of the lungs revealed dullness over the lower half of the right lung posteriorly, with markedly diminished breath and voice sounds over the right lower lobe. No signs of consolidation were elicited, and the left lung was essentially clear. The original chest roentgenogram showed evidence of a large right pleural effusion. The left heart border was found at the anterior line in the sixth intercostal space, but no rub, gallop, or significant murmurs were audible. The electrocardiogram showed a sinus tachycardia with evidence of myocardial disease. The liver and spleen were not palpable, and bowel sounds were hypoactive. There was massive pitting edema of the lower extremities and presacral region and abdominal wall, but no periorbital edema. The remainder of the physical examination was within normal limits.

A chest roentgenogram following thoracentesis showed a decrease in the size of the pleural effusion, but also demonstrated an abnormal gas shadow in the right upper quadrant suggestive of free air beneath the diaphragm. The roentgen findings were interpreted as evidence of either interposition of bowel between diaphragm and liver or, possibly, herniation of bowel into the right pleural cavity through the diaphragm. As studies were being undertaken to delineate the portion of the bowel affected, the patient's respirations suddenly became very labored and ceased while a tracheotomy was being performed. She had been in the hospital less than 30 hours. Although the results were not obtained before death, 5 of 6 ante-mortem blood cultures and the pleural fluid culture grew *C. perfringens*. Review of the literature reveals only 2 other reasonably well documented cases of primary pneumonia due to this organism.—T. H. NOEHREN

Allergic Pneumonitis in a 21-Month-Old Child (in Slovak). J. MICHALIČKOVÁ* and E. BREUER. *Brat Lek Listy*, October 15, 1958, 38: 411–416. (*Komenský U., Bratislava, Czechoslovakia)

A case of pneumonitis in a child is described. The offending allergen was not clearly demonstrated, but hyperleukocytosis with eosinofilia up to 80 per cent, hyperproteinemia with hypergammaglobulinemia, and increased reticular marking at roentgenographic examination were present. No infectious agent was found in spite of

repeated bacteriologic and virologic examinations. Corticotropin and cortisone treatment relieved the symptoms, but all returned when the corticoid therapy was discontinued. Later, all symptoms slowly and spontaneously disappeared. —J. Ilavsky

Clinical and Pathologic Contributions on Pneumonitis of the Cholesterol or Foam-Cell Type (in Italian). N. Belli*, G. Coppola, and V. Rustichelli. *Ann Ist Forlanini*, No. 2, 1959, 19: 143–174. (*Istituto C.Forlanini, U. of Rome, Italy)

The history of one rare case of pneumonitis of the cholesterol or foam-cell type in a 45-year-old male patient is given in some detail. The clinical, laboratory, roentgenographic, bronchographic, and bronchoscopic data are briefly given, particularly for diagnostic purposes. The gross anatomic, histologic, and histochemical findings obtained from the lung removed by surgery are described in more detail. The histopathologic picture was characterized by a productive inflammatory process in the pulmonary interstitial tissue, and by the presence in the residual alveolar spaces of numerous large foam cells, with a small pyknotic nucleus which was also often found in the larger bronchi. Histochemical studies showed that the vacuoles of this type of cell were full of lipids and gave positive reactions to Schultz's test for cholesterol and its esters. In this case, as in 2 others of pulmonary silicosis and cancer of the breast with pulmonary neoplastic lymphangitis, which are briefly discussed, the accumulation of lipids was due to the blockage of the lymphatic vessels with the subsequent massing into the intra-alveolar macrophages of the lipids which could not be metabolized and drained through the lymphatics. —I. Archetti

Pulmonary Alveolar Proteinosis. D. J. Carlson* and E. W. Mason. *Amer J Clin Path*, January, 1960, 33: 48–54. (*Milwaukee Hosp., Wisconsin)

On the basis of examination of sputum, i.e., its microscopic appearance and histochemistry, a tentative diagnosis of alveolar proteinosis was made. The clinical progression of the disease, the pulmonary function studies, roentgenographic findings in the lungs, the laboratory data, and the morphologic studies of the sputum were consistent with the diagnosis. If the sputum examination proves to be a valid means of laboratory examination, more cases of alveolar proteinosis may be recognized by other observers at a time more suitable for investigation than at autopsy. The technique is simple. Sputum is placed in formalin fixative, and sections are prepared by means of the usual histologic techniques. In addition, smears for cytologic study are prepared in the usual manner.—E. Dunner

Pulmonary Alveolar Proteinosis: Report of Three Cases. J. Sieracki*, R. Horn, and S. Kay. *Ann Intern Med*, October, 1959, 51: 728–747. (*Henry Ford Hosp., Detroit, Mich.)

Three new cases of pulmonary alveolar proteinosis are reported. The histologic findings in biopsy material from the lungs are essentially identical and do not differ from those originally detailed by Rosen and co-workers. The granular and crystalline inclusions in the proteinaceous intra-alveolar deposit that characterizes the disease are emphasized. Periodic acid-Schiff–positive material, similar to the amorphous intrapulmonary deposit, was found in phagocytes in the supraclavicular lymph nodes of 1 case. This study supports the concept that pulmonary alveolar proteinosis is a new disease, but a factor or factors common to all, or most, of the cases that might point to etiologic possibilities remains unidentified (after authors' summary).—T. H. Noehren

Myocardial Sarcoidosis, Complete Heart Block and Aortic Stenosis. R. Botti* and F. Young. *Ann Intern Med*, October, 1959, 51: 811–820. (*Western Reserve U., Cleveland, Ohio)

A case of complete A-V block secondary to sarcoid of the conducting system is presented. In addition, there was rheumatic carditis with focal Aschoff nodules and minor involvement of the aortic, mitral, and tricuspid valves. Sarcoid may involve the heart directly, or secondarily as a result of pulmonary disease. Pulmonary sarcoid may cause fibrosis, pulmonary hypertension, and cor pulmonale. Longcope and Freidman observed myocardial sarcoid in 20 per cent of the autopsied cases of sarcoidosis reported in the literature up to that time. Electrocardiographic manifestations include paroxysmal tachycardias, conduction defects, and left ventricular hypertrophy. Patients may die suddenly, have Stokes-Adams attacks, or other clinical features of heart block. Death from myocardial involvement occurs from 3 months to 15 years after the onset of clinical symptoms.—T. H. Noehren

Staphylococcal Bullae (in French). A. Charbonneau*. *Canad Med Ass J*, November 15, 1959, 81: 813–815. (*Hotel-Dieu St.-Vallier, Chicoutimi, Quebec, Canada)

Thirteen cases are discussed of bullae associated with staphylococcal pneumonia in young infants. Because of severe dyspnea and cyanosis, 7 cases (55 per cent) were treated surgically by needle

decompression followed by tube drainage. The procedure had to be repeated more than once in several patients. Supplementary therapy included oxygen by tent, tracheal suction, dependent drainage, superinone (Alevaire®), and antimicrobials. In 2 cases, Varidase® (a combination of streptokinase and streptodornase) was used with equivocal results. In 3 cases the development of empyema necessitated open drainage. One patient developed a purulent pericarditis. There were no deaths.—E. A. RILEY

Considerations on a Survey of Pulmonary Staphylococcal Infections (in Spanish). J. M. SALAS GINABREDA*. *An Med (Barcelona)*, No. 2, 1959, 45: 232–234. (*Hospital de Infecciones, Barcelona, Spain)

In October, 1959, a survey was made among a group of pediatricians pertaining to the incidence of pulmonary staphylococcal infections in their practices from 1947 until the present. Forty-four cases were collected: 84 per cent of the cases were in children up to 2 years of age, and 50 per cent were in children less than 1 year of age. Of these, 23 cases had pleural complications with empyema. Treatment consisted of antimicrobials including penicillin, chloramphenicol, erythromycin, and bacitracin, as well as surgical drainage of empyemas when present. There was an over-all 25 per cent mortality; mortality was highest in the patients less than 1 year old.—H. GARCÍA

Staphylococcal Pericarditis (in Spanish). J. ALBOS MARTINEZ*. *An Med (Barcelona)*, No. 2, 1959, 45: 201–205. (*Hospital de Infecciones, Barcelona, Spain)

Two cases are presented of staphylococcal pericarditis in children aged 9 and 10, respectively. In both patients, furunculosis preceded the onset of septicemia and pericarditis. Staphylococcal pericarditis is never an isolated finding, but occurs in the course of sepsis. The salient clinical symptoms and signs are persistent precordial pain aggravated by cough and respiratory movements, severe dyspnea, orthopnea, persistent tachycardia, pericardial friction rub and, later, signs of pericardial fluid accumulation. Friction rub appeared in both cases after antimicrobial therapy had been started. Both patients were treated successfully with a combination of antimicrobials which included tetracycline and erythromycin, and had uneventful recoveries. Neither needed surgical drainage. The possibility of constrictive pericarditis must be watched for in the follow-up study of these patients.—H. GARCÍA

The "Precordial Catch," a Syndrome of Anterior Chest Pain. A. MILLER* and T. TEXIDOR. *Ann Intern Med*, September, 1959, 51: 461–467. (*Michael Reese Hosp., Chicago, Ill.)

Twenty-eight patients with a distinctive anterior chest pain syndrome are reported. The syndrome, termed the "precordial catch," can be diagnosed from the typical history, the main characteristics of which are severe sharp pain occurring at rest or during mild activity, located near the cardiac apex, and lasting from ½ to 5 minutes. The pain is aggravated by deep inspiration, and the invariable reaction to its sudden onset is suspension of respiration. Breathing is then maintained in a shallow manner until the pain disappears. On occasion the pain is quickly relieved by a forced inspiration. The onset of the pain is often associated with a poor posture, and improvement of posture may ease it somewhat. This benign syndrome, of unknown etiology, has importance only in its differentiation from anterior chest pains of organic significance (after author's summary).—T. H. NOEHREN

Thoracic Organs Affected by Malignant Systemic Diseases of the Lymphatic System and Their Manifestations (in Czech). J. KOLÁŘ*, J. KÁCL, and L. PALEČEK. *Rozhl Tuberk*, January, 1959, 38: 43. (*Charles U., Prague, Czechoslovakia)

The authors discuss problems of roentgenographic symptomatology and the diagnosis of various diseases affecting the mediastinum, lungs, and pleura, and malignant tumors of the lymphatic system. They stress that accurate recognition of these diseases is not usually possible unless biopsy is performed.—J. ILAVSKY

Pulmonary Aspergilloma (in Czech). A. FINGERLAND*, O. SKŘIVÁNEK, F. MYDLIL, and J. PROCHÁZKA. *Cas Lek Cesk*, May 8, 1959, 98: 550–556. (*University, Hradec Králové, Czechoslovakia)

Eight cases of pulmonary aspergilloma were studied. The aspergilloma developed in bronchiectasia in 5 cases, in tuberculous cavities in 2, and in a chronic lung abscess in 1. It was not possible to establish the beginning and duration of these mycetomas. All of the cases were discovered accidentally, and were of more than a year's duration.—J. ILAVSKY

Pleural Mesothelioma: Case Report and Some Diagnostic Features. M. D. HAUST* and G. F. KIPKIE. *Canad Med Ass J*, December 1, 1959, 81: 918–922. (*Kingston General Hosp. and Queen's U., Ontario, Canada)

A case of diffuse pleural mesothelioma in a 52-year-old woman is presented. The clinical, pathologic, and roentgenographic findings in this type of tumor are discussed in detail.—E. A. RILEY

Thymic Tumors Associated With Cushing's Syndrome: Review of Three Cases. D. A. SCHOLZ* and R. C. BAHN. *Proc Mayo Clin*, September 2, 1959, 34: 433–442. (*Mayo Clinic, Rochester, Minn.)

A case is presented of malignant thymoma occurring in a patient who 9 months previously had subtotal adrenalectomy for Cushing's syndrome. Metastatic involvement of the superior vena cava and parietal pericardium resulted in the patient's death. The findings in 2 additional cases of Cushing's syndrome with thymic tumors previously reported from the Clinic are reviewed briefly (Authors' summary).—E. A. RILEY

Antibodies to *Haemophilus Influenzae* in Chronic Bronchitis. A. A. GLYNN*. *Brit Med J*, November 7, 1959, No. 5157: 911–914. (*St. Mary's Hosp., London, England)

A method is described of detecting antibodies to *H. influenzae* by the agglutination of tanned red cells coated with a sodium carbonate extract of the organism. With this method, antibodies in high titer (>500) have been found in 66 per cent of the patients with bronchitis, compared to similar though never quite such high titers in 21 per cent of asthmatic patients and 6 per cent of controls. Within the bronchitis group, titers bore little or no relation to the duration or severity of the disease or to the presence of active infection. The results confirm the close association of *H. influenzae* with chronic bronchitis, but lend no support to the theory that *H. influenzae* is responsible for the acute infective episodes which occur. The need for further study of *H. influenzae* antigens is stressed (after author's summary). —E. A. RILEY

Primary *H. Influenzae* Pneumonia in an Adult with Extreme Hyperpyrexia. R. SCHWIMMER*. *Amer J Med Sci*, December, 1959, 238: 713–719. (*Greenwich Hosp., Conn.)

A case of primary bacteremic *Hemophilus influenzae* pneumonia in a 49-year-old Negress is of particular interest in that severe hyperpyrexia (108.2°) occurred at the height of the disease, necessitating corticoid therapy in addition to multiple antimicrobials.—W. J. STEININGER

TUBERCULOSIS, PULMONARY

Repeated Middle Lobe Syndrome Caused by Calcified Hilar Lymph Nodes (in Japanese). T. YOSHIKAWA*. *Clin Radiol*, January, 1960, 5: 46–53. (*Nihon Med. College, Tokyo, Japan)

The case is reported of a 26-year-old male who had 3 attacks of fever, cough, sputum, and hemoptysis in a 13-month period. On each occasion the right middle lobe was involved and atelectatic. The patient expectorated two bean-sized calcified masses during the last episode, and then made a rapid recovery. Bronchoscopy demonstrated an ulcer on the posterior wall of the right main bronchus a few centimeters below the bifurcation after expectoration of the stones. Tubercle bacilli were demonstrated by fluorescent microscopy but were not recovered by animal inoculation and culture from the calcified material. The patient has not since had the same episode. It is concluded that the calcified hilar lymph nodes either outside of or in the bronchial wall were responsible for the recurrence of the middle lobe syndrome in this case.—I. TATENO

Remission of Long Duration in a Case of Tuberculosis with Amyloidosis (in French). H. BÉNARD*, L. JUSTIN-BESANCON, H. PÉQUIGNOT, S. DORMONT, and J. DORMONT. *Presse Med*, October 31, 1959, 67: 1883–1885. (*Paris, France)

This is a case report of systemic amyloidosis in a tuberculous patient. Following antimicrobial treatment, a remission of 28 months occurred, although bilateral pulmonary lesions persisted. Finally a relapse occurred and the patient died of renal failure. A review of the literature on this subject is given with a detailed report of the conditions under which the remissions occurred and the kind of therapy which had been applied.—E. LYON

The Effect of So-called Asian Influenza on Pulmonary Tuberculosis (in Finnish). K. LYYTIKÄINEN*. *Duodecim*, October, 1959, 75: 798–802. (*Deceased)

During the Asian influenza epidemic from October, 1957, to February, 1958, 181 patients with pulmonary tuberculosis or pleurisy were admitted to a sanatorium. Sixty (33 per cent) of them had had Asian influenza less than 2 months prior to admission. Of this group, 28 were readmissions in whom sputum became positive for *M. tuberculosis* after an asymptomatic interval of 1 to 10 years. While hospitalized, 116 patients contracted influenza. Roentgenographic deterioration was noted in 14 (12 per cent) of these patients within the first 2 months after the onset of the complicating disease. Five died within 2 months; the deaths were evidently influenced by the Asian influenza.—J. HAAPANEN

Pathologic Studies on the Formation of Tuberculous Cavities and Encapsulated Caseous Foci.

Report III (in Japanese). K. TAKA*, A. FUKUI, S. NAKAMURA, H. DAMBARA, Y. OGAWA, K. NISHI, M. HIRAYAMA, I. KOKUBO, K. TSUBOI, and M. TADANO. *Kekkaku*, January, 1960, 35: 24–28. (*Toneyama National Sanatorium, Osaka, Japan)

Encapsulated tuberculous caseous foci of several types are described. They are classified into the following 4 types according to the histologic findings, especially with regard to the structure of the reticular fibers in the caseous material stained by silver impregnation. Type A focus is structureless, and type B focus shows the structure of normal alveoli. Marked proliferation of the reticular fibers is demonstrated in type C focus. Type D focus shows a structure simulating an annual ring of a tree.

It is believed that encapsulated caseous foci may arise in several ways: Type A focus may be produced from a completely blocked tuberculous cavity with resultant inspissation of caseous material, or from a localized softened material which is caused by the softening of a primary exudative lesion with extensive leukocytic infiltration. Type B focus may arise from the encapsulation of a primary exudative lesion without leukocytic infiltration. Type C focus may arise from the encapsulation of a productive lesion without extensive leukocytic infiltration as in type B. Type D focus, namely the annular type, may be produced from the centrifugal expansion caused by repeated caseation of a focus. The pathogenesis of encapsulated caseous foci are discussed in conformity with histologic features and many experimental results (after authors' summary). —I. TATENO

Characteristics of Pulmonary Tuberculosis in Children Compared between 1937 to 1939, and 1955 to 1957 (in Italian). A. TOGNERI* and A. UBEZIO. *G Ital Tuberc*, November–December, 1959, 13: 395–404. (*Sanatorio, Prasomaso, Sondrio, Italy)

The characteristics of pulmonary tuberculosis in a group of 389 children, 3 to 14 years of age, observed from 1937 to 1939 (a period before the introduction of antimicrobials) were compared with those of another group of 458 children of the same age who were observed from 1955 to 1957, when antimicrobials were largely in use. These elements were taken into consideration: sex, age, environment, manner of onset of the disease, temperature, weight variations, presence of tubercle bacilli, forms of tuberculosis and specific complications during hospitalization, nature of treatment and its results, and length of hospitalization. The forms of disease observed in the second group were less serious and showed a limited tendency either to evolve or to give dissemination: the number of complications, both pulmonary and extrapulmonary, was therefore much smaller. It is concluded that treatment with isoniazid, both alone and combined with other antimicrobials, was best, especially because of the good tolerance to this drug.—I. ARCHETTI

On the Immunological Reactivity of Tuberculous Patients. G. L. WILKENS* and A. TASMAN. *Brit Med J*, December 12, 1959, No. 5162: 1305–1307. (*University Hosp., Utrecht, Holland)

Sixteen tuberculous patients and 11 healthy controls were given two intramuscular injections of tetanus phosphate toxoid. Antitoxin titers were found to be markedly lower in the tuberculous than in the control group.—E. A. RILEY

A Study of the Autonomic Nervous System in Tuberculous Patients during Isoniazid Treatment in Mountain and Lowland Environments (in Slovak). B. KUKLOVÁ-ŠTÚROVÁ*, M. KRIŽANOVÁ, and M. BABÁL. *Brat Lek Listy*, February 15, 1959, 39: 148–153. (*Komenský U., Bratislava, Czechoslovakia)

Electrocardiographic recordings were used by the authors for this study of the autonomic nervous system. The patient rested for 15 minutes in the horizontal position, and then 10 heart cycles were recorded. Then the patient stood for 1 minute, and during this period six 5-second recordings were taken. The patient then resumed the resting position again and the 5-second recording was continued in 5-second intervals. Examinations and recordings were repeated a few times in 12 weeks. In the high-altitude group of patients, there was a definite tendency toward stabilization of the autonomic system reactions. In the lowland group there was a definite increase of the autonomic system reactions, especially those of the sympathetic. Isoniazid in doses of 5–10 mg. per kg. of body weight has little effect upon the tonus as well as the excitability of the autonomic nervous system measured in 3 precardial zones. The changes observed in patients are due to reparative processes.—J. ILAVSKY

Prognosis in Minimal Pulmonary Tuberculosis (in Slovak). O. HALÁK* and E. CHALUPOVÁ. *Brat Lek Listy*, February 15, 1959, 39: 154–159. (*Army Institute for Pulmonary Diseases, Nová Polianka, Czechoslovakia)

The prognosis in 87 patients with minimal pulmonary tuberculosis was studied and analyzed; 75 per cent were less than 30 years of age. The diagnosis of tuberculosis was made in almost 50

per cent by chance or during screening for tuberculosis in the army; 42 per cent had no subjective complaints at all; 44.6 per cent were released from the hospital with completely restored working ability and, at the time of report, 83.9 per cent were able to work. Progression was observed in 19.5 per cent, mostly during the first 4 years. —J. Ilavsky

Respiratory and Adrenocortical Function in Pulmonary Tuberculosis (in Japanese). M. Imaizumi*, S. Watanabe, H. Yokota, T. Haga, H. Koyama, and H. Okaniwa. *Clin Resp Organs*, January, 1960, 15: 27–34. (*National Tokyo Sanatorium, Kiyose, Japan)

The writers studied the correlation between respiratory function (expressed in terms of percentage of "normal" vital capacity) and adrenocortical function. There was a positive correlation between the percentage values of "normal" vital capacity and 17-ketosteroids excreted in the urine. Adrenocortical reserve function was studied by examining the excretion of 17-ketosteroids following injection of corticotropin. Mean values of 17-ketosteroids decreased in parallel with the decrease in vital capacity. Excretion of 17-hydroxycorticoids did not show as clear-cut a correlation with the vital capacity as did the 17-ketosteroids. It is concluded that adrenocortical function parallels respiratory function.
—I. Tateno

Tuberculosis Occurring During Steroid Therapy. J. MacKinnon*. *Brit Med J*, December 11, 1959, No. 5163: 1375–1379. (*U. of Manchester, England)

Three patients who developed tuberculosis during steroid therapy are discussed. In 2 the disease was widely disseminated. The importance of considering this complication in any patient who deteriorates unexpectedly while receiving steroids, and the difficulties of diagnosis, are stressed. Precautions before and during treatment are suggested, and the question of prophylactic antituberculosis chemotherapy is discussed (after author's summary).—E. A. Riley

TUBERCULOSIS, NONPULMONARY

Rupture of Tuberculous Aortic Aneurysm into Lung. N. DeProphetis*, H. V. Armitage, and E. D. Triboletti. *Ann Surg*, December, 1959, 150: 1046–1051. (*Chester Hosp., Penn.)

The first case is reported of a tuberculous aortic aneurysm rupturing into the lung and treated surgically. Evidence pointed to duodenal bleeding, and a gastrectomy was done. At a second operation, the bleeding was found to be from an aortic aneurysm that had ruptured into the lung. This was treated by lobectomy and resection of the aneurysm. The patient died suddenly at home 1 month later. Autopsy revealed a rupture of a second aneurysm that had developed below the site of resection of the first. Tuberculous aortitis is extremely rare, and even more rarely does a resulting aneurysm rupture into the lung, such a case never having been reported previously. The picture was further obscured by absence of roentgenographic evidence of pulmonary tuberculosis, 3 sputum specimens negative for acid-fast organisms, hemoptysis that was first swallowed and then presented as hematemesis, a normal chest roentgenogram, an history of ulcer, and demonstration of the ulcer by roentgenogram and at gastrectomy. Although granulomas were seen in the aortic tissue obtained at thoracotomy, a definite tuberculous etiology was not established until the day before death, when a positive culture was obtained. This was corroborated by identifying acid-fast organisms in tissue sections. —M. J. Small

Failure of Treatment for a Chronic Diphtheria Carrier Condition in a Patient with Laryngeal and Palateal Lupus Vulgaris (in Czech). P. Dostál*. *Rozhl Tuberk*, November, 1958, 18: 680–682. (*Hospital, Jablonec nad Nisou, Czechoslovakia)

A 36-year-old woman with pulmonary tuberculosis and lupus vulgaris was found to be a carrier of a toxic strain of *Corynebacterium diphtheriae*. Because this woman infected her daughter with diphtheria, the author tried to cure her of the carrier condition. But uninterrupted 2-month treatment with antidiphtheria serum, anatoxin, penicillin, chloramphenicol, erythromycin, bacitracin, and tyrothricin was a complete failure. —J. Ilavsky

Tuberculoid Granulomas in the Oral Mucosa and Cervical Lymph Nodes: South American Blastomycosis (in German). T. Wegmann* and H. U. Zollinger. *Schweiz Med Wschr*, October 31, 1959, 89: 1151–1153. (*Kantonsspital, St. Gallen, Switzerland)

A cabinet maker had been exposed to dust from tropical woods for many years, first in Brazil, later in Switzerland. He consulted a doctor because of a slowly growing tumor on the neck. The examination revealed ulcerations and granulations on the buccal mucosa, and pulmonary infiltrations. Diagnosis of South American blastomycosis (Almeida's disease) was made only by histologic examination of 3 biopsy specimens from the mouth and lymph nodes, and by cultures for fungi. Since there was no traumatic lesion

in the mouth, the infection was supposed to have occurred by air.—J. HAAPANEN

Microbiologic Diagnosis in Tuberculosis of the Female Genital Organs (in Slovak). R. GRIGEROVA*. *Lek Obzor*, October, 1959, 8: 589–594. (*Tuberculosis Research Institute, Bratislava, Czechoslovakia)

During the years 1956 and 1957, the author tested 722 samples of menstrual blood from 259 patients with chronic adnexitis: 81 specimens positive for tubercle bacilli were obtained from 32 patients. Of the samples tested, 12 were positive only by culture, 27 were positive both by culture and in the guinea pig, and 42 were positive only in the guinea pig. Microbiologic examination of the menstrual blood should be repeated at least 3 or more times. Examination of vaginal and cervical secretions gave a considerably lower percentage of positive results.—J. ILAVSKY

Investigations into Tuberculosis of the Genitourinary Tract. C. P. WU*, K. C. LIU, and C. T. SUN. *Chin Med J*, November, 1959, 79: 428–436. (*Peking Med. College, China)

Data have been collected on 1,820 cases of genitourinary tuberculosis seen in various hospitals. Sixty-two per cent of the patients were males, and 66 per cent were in the age group between 20 and 40 years. Eighty-one per cent complained of urinary frequency, and 71 per cent of hematuria. Sixteen per cent of the collected cases revealed contralateral hydronephrosis. Retrograde pyelograms revealed changes diagnostic of tuberculosis in 19 per cent of the cases. From 29 to 51 per cent of the cases in the various hospitals did not reveal characteristic roentgenographic findings of tuberculosis with excretory urography because of impaired renal function. Examination of semen and prostatic fluid for tubercle bacilli was found to be of value. Therapy included streptomycin, nephrectomy, partial nephrectomy, and local excision of the tuberculous lesion in the kidney. The operative mortality rate for 1,971 nephrectomies performed in the last 10 years at 16 hospitals was 0.15 per cent. Postoperative tuberculous sinuses occurred in 2.7 per cent. —L. HYDE

The Prognosis of Genito-urinary Tuberculosis: A Review of 818 Cases. G. L. GALE* and W. K. KERR. *Canad Med Ass J*, December 15, 1959, 81: 977–982. (*Toronto Hosp. for Tuberculosis, Canada)

Although pulmonary and orthopedic tuberculosis are decreasing in frequency, 422 new cases of genitourinary tuberculosis were admitted to the Toronto Hospital for Tuberculosis between the years 1947 and 1958, compared to 347 new cases admitted between the years 1932 and 1947. A series of 818 cases of genitourinary tuberculosis treated in or associated with the Toronto Hospital is presented. The first series of 82 cases treated with nephrectomy or chemotherapy was followed up for 20 to 35 years, and thus represents the natural history of the disease. The second series of 347 cases treated with nephrectomy as indicated, but without chemotherapy, was followed up for zero to 15 years. The third series of 389 cases treated with both nephrectomy as indicated and chemotherapy was followed up for 1½ to 11½ years.

Twenty-six patients (32 per cent) of the first group are alive and well; 56 patients (68 per cent) have died: 27 per cent of renal tuberculosis, 31 per cent of nonrenal tuberculosis, and 10 per cent of other causes. Among the second group, 182 patients (52 per cent) died, with 10 per cent due to renal tuberculosis, 36 per cent due to nonrenal tuberculosis, and 6 per cent due to nontuberculous causes. Among the 389 who received chemotherapy, there were 246 males and 143 females; the ages varied from 2½ to 79 years; 134 patients had active pulmonary tuberculosis, 130 had inactive pulmonary or pleural tuberculosis, 125 had no pulmonary or pleural disease, and 121 had extrapulmonary tuberculosis. The patients with associated male genital tuberculosis included 124 cases of tuberculous epididymitis, 33 cases of prostate involvement, 34 cases of seminal vesicle involvement, and 5 cases of testicular involvement. The extent of renal involvement following Lattimer's classification was minimal in 86 cases (22 per cent), moderate in 189 (48 per cent), and advanced in 94 cases (24 per cent).

Surgical treatment, which has been performed much less frequently since 1953, consisted of nephrectomy in 157 cases (40 per cent), heminephrectomy in 4, orchidectomy in 33, epididymectomy in 16, ureterostomy in 4, uretero-sigmoid transplant in 2, and ileocystoplasty in 7. In this group, 285 patients (74 per cent) are alive and well, 34 (8 per cent) are in poor health or still under treatment, and 67 (17 per cent) are dead. Less than 6 months of chemotherapy was received by 175 patients, resulting in a 22 per cent relapse rate and 29 per cent mortality; 51 received less than 12 months' chemotherapy, with an 8 per cent relapse rate and 20 per cent mortality; and 163 received more than 12 months of chemotherapy, with a 1.3 per cent relapse rate and 4 per cent mortality. In this last group, none of the deaths was due to renal tuberculosis. Although prior to chemotherapy the extent of involvement was the single most important prognostic factor, this factor is of less importance than the duration of

chemotherapy. All patients now receive triple-drug therapy for 18 to 24 months.—E. A. Riley

Abdominal Manifestations of Lumbar Pott's Disease (in French). S. de Séze*, J. Welfling, and C. Guérin. *Presse Med*, October 31, 1959, 67: 1885–1890. (*Paris, France)

It is pointed out that certain forms of tuberculosis of the lumbar spine manifest themselves with violent abdominal pain and often mask the vertebral condition. Five such cases are reported. Such symptoms may lead to a false diagnosis and sometimes even to exploratory abdominal surgery. The pathogenesis of such symptoms is discussed. It is, therefore, advisable to do roentgenographic studies of the spine in the presence of such symptoms, even if there are no symptoms pointing to the vertebrae.—E. Lyon

Endocranial Calcifications in Patients after Tuberculous Meningitis. Their Relationship to Prognosis in the Disease (in Italian). C. Caione*. *Ann Ist Forlanini*, No. 2, 1959, 19: 204–217. (*Istituto Forlanini, Rome, Italy)

The cranial roentgenographic aspect of 42 children and adolescents who had had tuberculous meningitis 2½ to 10 years ago was studied. Twelve of these patients had been treated with streptomycin alone, the remaining 30 with streptomycin in association with isoniazid. None had shown endocranial calcifications early after recovery; however, they were found in 19 per cent of the patients at the time of the present study. Alterations in the sella turcica were not found. The number and extension of these calcifications, which generally appeared 2 years after recovery, were directly dependent on the seriousness of the sequelae of the disease, and were more often found in patients who were treated late and inadequately.—I. Archetti

Evaluation of Ophthalmologic Findings in Tuberculous Meningitis (in Czech). J. Velický* and R. Neumann. *Cas Lek Cesk*, June 19, 1959, 98: 785–789. (*Sanatorium, Nový Smokovec, Czechoslovakia)

The significance of finding tuberculous nodes and changes in the optical nerve papilla was evaluated in a statistical review of 173 children with tuberculous meningitis. It was concluded that tuberculous nodes on the eye fundus have no prognostic value. However, they are a very important aid in differential diagnosis. Conversely, edema of the papilla is an atypical symptom, but it is closely related to the clinical course as well as to the incidence of neurologic complications and, therefore, is very important for prognosis.—J. Ilavsky

Conservative Therapy in Skeletal Tuberculosis: An Appraisal Based on Experience in South Africa. C. J. Kaplan*. *Tubercle*, October, 1959, 40: 355–368. (*Addington Hosp., Durban, South Africa)

This study concerns 259 cases of Potts' disease in childhood. It is concluded that the need for enforced, uninterrupted, and prolonged immobilization in bone and joint tuberculosis is probably not as important as has been taught. The results in Potts' disease even before the introduction of antituberculous drugs compare favorably with those obtained in Britain by the classic method in a similar period. Joint disease treated with specific therapy can proceed to a satisfactory termination without immobilization. Streptomycin and isoniazid have certainly shortened the duration of hospital treatment, and lowered both the death rate and the relapse rate in skeletal tuberculosis. The extent of spinal involvement appears to have been limited by these drugs, and the percentage of cases showing bony fusion has been increased. The incidence of paraplegia has remained substantially the same, but the results have been significantly improved. Intra-articular streptomyclideneisonicotinylhydrazine (Streptohydrazid®), which gives a high local concentration of the two most potent antituberculous agents, has shortened the clinical course in joint disease. It is of value even in severely involved joints as the patient is ready for surgery at an earlier date. An early prognosis of functional recovery can be made from the clinical and roentgenographic appearance of a joint at the commencement of treatment. This assists the early selection of cases for operation and also avoids unnecessary arthrodesis in the remainder. Effective treatment of bone and joint tuberculosis is possible in hospitals which are quite austere in their simplicity. The cost of such treatment is low by any standard.

The modern trend in the treatment of tuberculosis is to forsake the safe waters of conservatism for the uncharted seas of radical surgery. On the basis of the author's experience in many hundreds of cases, he finds that in skeletal tuberculosis conservative therapy is the treatment of choice. This view is strengthened by the circumstances which prevail in South Africa and to a greater or lesser extent in underdeveloped regions throughout the world, where the number of cases now being diagnosed exceeds earlier predictions of the incidence of the disease.—M. J. Small

UPPER RESPIRATORY TRACT DISEASE, VIRAL

Respiratory Illness in Children Simultaneously Infected with Hemadsorption Virus Type 1 and a Newly Recognized HeLa Enterovirus (HE). H. G. Crambletт*, J. A. Kasel, and J. P. Utz. *AMA J Dis Child*, November, 1959, 98: 578. (*National Institute of Allergy and Infectious Diseases, Bethesda, Md.)

This report describes etiologic studies on an outbreak of undifferentiated respiratory disease which occurred in a children's convalescent hospital in June, 1956. From the washings of anal swabs of ill children, a cytopathic agent (HE virus) was isolated in HeLa-cell cultures. Serologic and virologic studies indicated that this virus was not related to previously described viruses, and that it had the properties of an enterovirus. In several serums, antibody responses were such as to suggest simultaneous infection with Type 1 hemadsorption virus. There is support for the speculation that the clinical illnesses were the result of simultaneous infections with HE virus and Type 1 hemadsorption virus. Only additional studies and observations will establish the relationship between infection with HE virus and human illness.—M. J. Small

THORACIC SURGERY

Dissecting Aneurysm of the Aorta Treated Surgically. E. Rubin*, M. Rubin, and B. Seidenberg. *Amer J Med*, September, 1959, 27: 501–507. (*Montefiore Hosp., New York, N. Y.)

A case is described of a 62-year-old man with antecedent hypertension, arteriosclerosis, psoriasis, and psoriatic arthritis, in whom a diagnosis of dissecting aneurysm of the aorta was made. This was subsequently confirmed by angiocardiography. Fenestration to the aorta was performed in which a double-barrelled channel was established to enable the blood from the aneurysm to re-enter the main stream. The patient was discharged 10 days after operation in good condition. Two weeks later, because of epigastric pain, blood in the stool, and spitting of bright red blood, he was readmitted to the hospital. His condition worsened and he died the same day. It was suspected that the cause of death was proximal extension of the dissection, possibly involving the pericardium and causing heart tamponade. Autopsy was not performed. The available case reports on the surgical treatment of dissecting aneurysm of the aorta are reviewed (Authors' summary).—T. H. Noehren

Scalene Node Biopsy. R. L. Aikens*. *Canad Med Ass J*, December 1, 1959, 81: 891–893. (*Dalhousie U., Halifax, Nova Scotia)

One hundred cases in which scalene lymph node biopsy was performed between 1951 and 1958, inclusive, were reviewed. Cases with palpable cervical lymph nodes were not included in the 100. In 27 cases the method provided a specific diagnosis. In 22 cases with the clinical features of pulmonary sarcoidosis, scalene node biopsy confirmed this diagnosis in 15. In 35 cases of primary carcinoma of the lung, scalene node biopsy was positive in 8. In 15 per cent of the cases no lymphoid tissue was found. Mediastinal extension of the biopsy was not carried out. The fact that in 15 per cent of the cases no lymph nodes were found might be due to lack of experience with the procedure on the part of the surgeon. Occasionally, the histologic picture of the scalene node may not represent the disease actually present.
—E. A. Riley

Cancer of the Lung in Women. R. Ottoman* and J. Stein. *Calif Med*, January, 1960, 92: 38–39. (*U. of California, Los Angeles)

Cancer of the lung in women has the same signs and symptoms as in men, but the disease seems to advance more rapidly. Among 283 patients with lung cancer observed between April, 1955, and December, 1958, 35, or about 1/8, were women. In 15 no surgical treatment was considered because the disease was already far advanced. Of the remaining 19, only 5 underwent definitive operation. All but 1 of the 35 patients were treated: 29 by radiotherapy, 2 with nitrogen mustard, and 3 with only palliative radiation of metastatic lesions. For all, the median survival time was 26 weeks; 7 were alive 1 year later.—E. A. Rouff

Use of Sochor's Controllable Catheter in the Treatment of Chronic Cavities (in Slovak). M. Babál* and V. Čermák. *Rozhl Tuberk*, November, 1958, 18: 647–652. (*Komenský U., Bratislava, Czechoslovakia)

Sochor's controllable pulmonary catheter was used for local treatment of chronic tuberculous cavities. A solution containing 0.5 gm. of streptomycin and 150 mg. of isoniazid was administered twice a week into the draining bronchus or, when possible, directly into the cavity. This treatment was given an average of 18 times to each patient. Peroral antimicrobial therapy was given concurrently. The therapeutic results were encouraging. The treated cavity closed in 5 cases, diminished in 8, and remained unchanged in 1 patient. Soon after the start of treatment, sputum became negative in 10 patients.—J. Ilavsky

Diaphragmatic Hernia in Infancy. J. REED* and E. LANG. *Amer J Roentgenol*, September, 1959, 82: 437–449. (*Children's Hosp. of Michigan, Detroit)

This paper is based on a series of 48 cases of diaphragmatic hernia, all of which were subsequently confirmed either at the time of operation or at autopsy. Emphasis is placed on the important factors in pleuroperitoneal hernia, which is the most common type of diaphragmatic hernia and also the type most dangerous to the infant. The condition must be kept in mind as a possible basis for respiratory embarrassment. Plain roentgenograms are almost always diagnostic. A mass is demonstrated in the lower ½ to ⅔ of the hemithorax, usually showing fluid levels, displacement of the mediastinum to the opposite side, absence of a visible diaphragm on the side, absence of gas-filled intestine in the abdomen and, usually, an esophagus of normal length. The possibility that the lung may be aplastic or hypoplastic rather than merely atelectatic should be considered. —T. H. NOEHREN

Pulmonary Embolus with Foreign Body in a Case of Broken Femoral Catheter (in Swedish). H. KNUTSON* and K. STENBERG. *Nord Med*, October 8, 1959, 62: 1491. (*Sahlgrenska Sjukhuset, Göteborg, Sweden)

Seven days after the removal of a femoral catheter, an 81-year-old male patient suddenly died. A pulmonary embolus containing a broken-off piece of the tubing was found at autopsy. The tubing had been thrown away without any further examination. Radiopaque tubing is recommended for any intravascular use to aid the localization of any subsequently detached fragments. —J. HAAPANEN

The Diagnosis and Classification of Mediastinal Masses. 1. A Study of 782 Cases. H. LYONS, G. CALVY, and B. SAMMONS. *Ann Intern Med*, November, 1959, 51: 897–932. (*State U. of New York, Downstate Med. Center, Brooklyn)

Mediastinal masses may be neoplastic or non-neoplastic. The neoplasms may be benign or malignant, and are dangerous especially when undiagnosed. Because of the close contact of vital structures in the mediastinum, threatening complications can occur, and the possibility of malignancy is always present with a mediastinal tumor. Of the present entire group of 782 cases, 42 per cent were histologically malignant, and many others were life endangering because of size or position. The mediastinal tumors must be differentiated—and usually can be—with the use of modern diagnostic aids. Scalene node biopsy and angiocardiography are two essential diagnostic procedures, and their use may prevent needless exploratory thoracotomy. Angiocardiography gives information about the feasibility of operation or, in fact, evidence to contraindicate an operation. Thoracotomy is mandatory, and should not be delayed when other methods cannot establish the diagnosis. Thoracotomy has a low case fatality rate, offers cure in benign lesions, and gives accurate information on the histologic nature and the gross involvement by the tumor. This permits intelligent management and provides valuable information for prognosis (after authors' summary).—T. H. NOEHREN

Endoscopic Thoracic Sympathectomy. H. A. ROEDLING* and C. S. MACCARTHY. *Proc Mayo Clin*, September 16, 1959, 34: 460–466. (*Mayo Clinic, Rochester, Minn.)

The technique of endoscopic thoracic sympathectomy is described briefly and suggested as an alternate method of accomplishing thoracic sympathectomy, with the objective of reducing morbidity and mortality rates and thus broadening the application of surgery of the sympathetic nerves to include cases in which this type of surgery heretofore was not considered acceptable or desirable. A case is presented in which this technique was employed to good advantage (Authors' summary).—E. A. RILEY

The Scalenus Anticus Syndrome. I. (in Danish). P. RASMUSSEN* and N. G. SIMONSEN. *Nord Med*, October 29, 1959, 62: 1569–1571. (*Kommunehospitalet, Århus, Denmark)

The etiologic factors of the scalenus anticus syndrome are discussed. The problems of differential diagnosis are presented and, in particular, Adson's test and infiltration anesthesia of the scalenus anticus muscle as a means of differential diagnosis are described. The results of conservative and surgical treatment are compared, but it is emphasized that they are not directly comparable, since conservative therapy is generally used in the early or easy stages, and surgery in cases with severe neurologic or vascular symptoms.

The Scalenus Anticus Syndrome. II. Results of Operative Treatment in 20 Cases, Including 16 with the Costa Cervicalis Syndrome: pp. 1572–1573.

Scalenotomy was done in 20 patients with the scalenus anticus syndrome, in 9 the cervical ribs were also extirpated or resected, and in a further 8 a fibrous string was cut. Fourteen patients recovered or improved markedly.—J. HAAPANEN

Diagnosis of Bronchogenic Carcinoma: An Evaluation of Pulmonary Cytology, Bronchoscopy and Scalene Node Biopsy. W. UMIKER*. *Dis Chest*, January, 1960, 37: 82–90. (*V. A. Hosp., Ann Arbor, Mich.)

A positive reaction in cytologic examination was the only microscopic evidence of carcinoma in more than 40 per cent of resected neoplasms of the bronchus, and more cancers were detected by this method than by bronchoscopy and scalene node biopsy combined, unless bronchoscopy included the cytologic examination of bronchial secretions. Positive or suspicious smears were obtained from 44 of 94 cases by a single cytologic examination of the sputum. The percentage of positive smears increased to 71 per cent when 3 specimens were examined, and to 96 per cent when more than 5 were studied. It was of greatest value in lesions of the upper lobes or in peripheral carcinomas. Anterior scalene node biopsy was positive in only 22 of 78 patients and was of most value in the diagnosis of undifferentiated or adenocarcinoma of the upper lobes.—E. A. ROUFF

Unsuspected Bronchogenic Carcinoma. J. PATE*, R. CAMPBELL, and F. HUGHES. *Dis Chest*, January, 1960, 37: 56–60. (*V. A. Hosp., Memphis, Tenn.)

This is a report of 32 cases of bronchogenic carcinoma in which the correct diagnosis was never seriously considered before death. These errors occurred in 650 cases of bronchogenic carcinoma from approximately 150,000 admissions. Joint pain and neurologic and gastrointestinal symptoms were present in most cases. Respiratory symptoms were the presenting complaints in only 2.—E. A. ROUFF

Thoracic Choriocarcinomas. P. THIBAULT*. *Presse Med*, October 31, 1959, 67: 1892–1894. (*Paris, France)

Thoracic choriocarcinomas are rare and highly malignant. They may be primary tumors located in the mediastinum or, more often, secondary and located in the lungs. In women they often occur in connection with pregnancy, frequently following a mole. However, these tumors may also appear after an abortion or delivery which did not indicate any abnormalities. The prognosis is, with very few exceptions, fatal and no effective treatment is known. The primary choriocarcinoma is usually located in the uterus; however, it may also occur in the ovaries or other organs. It is difficult to present statistics, as the histologic criteria for the diagnosis of choriocarcinomas vary.—E. LYON

ROENTGENOGRAPHY

Residual Cavities following Pulmonary Abscesses (in Czech). J. ŘEHOŘ*, L. STEINHART, J. KASALICKÝ, and J. KOLÁŘ. *Čas Lek Cesk*, May 8, 1959, 98: 563–567. (*University, Hradec Králové, Czechoslovakia)

Forty-two cases of pulmonary abscesses were periodically controlled from 2 to 11 years. In 7 cases (12 per cent), residual cavities remained and persisted. However, these residual cavities did not cause any trouble to the patients, and reinfection did not occur even after repeated catarrhs of the upper respiratory passages. Residual cavities following pulmonary abscesses are not considered an indication for resection.—J. ILAVSKY

Etiologically Unidentified Hilar Adenopathies (in Italian). G. NAIFOVINO* and P. BATTISTELLA. *Ann Med Sondalo*, July–August, 1959, 7: 223–244. (*Villaggio Sanatoriale, Sondalo, Italy)

The clinical histories of 3 cases of benign isolated hilar adenopathies in young, tuberculin-negative women are given in detail with the laboratory and roentgenographic data. In 2 patients the adenopathy was bilateral, while in the third it was unilateral. The enlarged lymph nodes were stationary during the first 3 to 5 months, and slowly decreased thereafter to become normal within 6 to 8 months after the start of observation. No involvement of other organs was found. All 3 cases were treated with streptomycin combined with isoniazid and prednisone. Diagnosis was uncertain, and it is believed that these cases must possibly be considered as forms of sarcoidosis. —I. ARCHETTI

Experience with Two New Media in Angiocardiography. A Preliminary Report. A. LEWITAN* and I. KROOP. *Amer J Roentgenol*, November, 1959, 82: 779–783. (*Jewish Chronic Disease Hosp., Brooklyn, N. Y.)

Two new, water-soluble contrast agents, methylglucamine diatrizoate (Cardiografin®) 85 per cent and 90.5 per cent have been employed in angiocardiographic and other roentgenographic diagnostic studies in a total of 29 patients. With few exceptions, diagnostic roentgenograms were obtained with each contrast medium. The quality of contrast provided by these concentrations of Cardiografin, and the paucity of unwanted side reactions attending their use, indicate that they are highly satisfactory media for use in angiocardiographic and other intravenous roentgenographic procedures for the diagnosis and study of cardiac and related conditions in both children and adults.—T. H. NOEHREN

The Diagnosis of Pericardial Effusion with Intracardiac Carbon Dioxide. J. H. SCATLIFF*, A. J. KUMMER, and A. H. JANZEN. *Radiology*, December, 1959, 73:871–883. (*Yale–New Haven Med. Center, Conn.)

A series of 22 patients was examined by the intravenous carbon dioxide insufflation technique in order to differentiate pericardial effusion and cardiac enlargement. With the patient in left decubitus, an opaque band is outlined roentgenographically between the carbon dioxide bubble in the right atrium and the overlying lung. The width of this band is increased in the presence of pericardial effusion or thickening. Correlation with the clinical or autopsy findings appears to bestow high diagnostic acceptability on the procedure. The method can be used with rapid filming devices or the usual equipment of a general roentgenography department if several features of diagnosis are kept in mind. The examination can be performed easily and appears to be without hazard in the cooperative patient.—W. J. STEININGER

Value of Pneumomediastinum in the Differential Diagnosis of Mediastinal Diseases (in German). J. LISSNER*. *Fortschr Rontgenstr Nuklearmed*, October, 1959, 91: 445–456. (*Universitätsklinik, Frankfurt/Main, Germany)

Roentgenograms are presented of 9 cases before and after the establishment of a pneumomediastinum. The unquestionable value of the procedure is discussed on the basis of the experience gained in 39 patients.—J. HAAPANEN

Diagnostic Pneumopericardium: Its Clinical Application. E. MAURER* and F. MENDEZ, JR. *Dis Chest*, January, 1960, 37: 13–22. (*U. of Cincinnati College of Med., Ohio)

Simple roentgenographic evaluation of the mediastinal and contiguous cardiac and pulmonary structures is frequently extremely difficult and in many instances may be impossible. The preoperative differential diagnosis of paracardiac lesions, even with barium in the esophagus and after angiocardiographic techniques, has presented a problem in the past. On the basis of experiments relating to the physiologic effects of the introduction of air into the intact pericardial sac in the laboratory, a simple safe technique for the introduction of air into the pericardial sac for diagnostic purposes has been evolved and applied in a series of patients. The preoperative information obtained by this procedure has been found to permit a direct, accurate, and less time-consuming surgical approach to lesions in and about the heart and mediastinum.—E. A. ROUFF

Incidence of Neoplasia after Irradiation of Thymic Region. H. LATOURETTE* and F. HODGES. *Amer J Roentgenol*, October, 1959, 82: 667–677. (*U. of Michigan, Ann Arbor)

From 1932 to 1951, the thymic regions of 958 patients were irradiated at the University Hospital. The dosage used was relatively low. Information on the subsequent course of 867 is known. Of this group, 99 are dead. Two patients developed a lymphoblastoma; 1, a leukemia; and 1, lymphosarcoma. This incidence of lymphoblastoma is somewhat higher than might be expected, but not significantly so. One patient developed thyroid carcinoma, which constitutes a statistically significant increase in the expected incidence rate. These findings are further suggestive evidence of some increase in the incidence of neoplasia after irradiation of the thymic region (after authors' summary).—T. H. NOEHREN

Arteriographic Findings in Coronary Sclerosis. L. DI GUGLIELMO*. *Acta Radiol (Stockh)*, November, 1959, 52: 369–378. (*Sodersjukhuset, Stockholm, Sweden)

The morphology of coronary arteries at different ages and the features of coronary sclerosis are presented. A study employing thoracic aortography and angiocardiography was made on 549 patients with congenital and acquired heart disease.

Coronary alterations induced by age have been investigated. Up to 15–20 years of age, the arteries present no sinuosity, outlines are sharp and smooth, and the diameter gradually and uniformly tapers toward the periphery. From 20–40 years of age, the arteries form sinuosities. The arteries are still sharply and smoothly outlined, and their diameters increase in proportion to the size of the heart. After 40 years of age, the sinuosities are more obvious. The increase in diameter is usually not proportional to the heart size, and the lumen becomes cylindric with no normal slow decrease in size as one progresses to the periphery.

Coronary arteriography in coronary sclerosis may be of some value. Three stages are reported. In the initial stage when no electrocardiographic changes or clinical symptoms are present, arteriography may demonstrate the only changes actually present. At a later stage when alterations may be noted on the electrocardiogram, the arteriogram readily shows the location and extent of alterations. In the still later stage when clinical data and electrocardiograms present the most marked findings, arteriography readily gives the following information: (*1*) extent and location of infarction, (*2*) condition of the other coronary branches, (*3*) evidence of collateral circulation and,

(4) detection of coronary obstructions not responsive to electrocardiography.—E. SHABART

Primary Lymphosarcoma of the Lung (in German). W. SCHULZE*. *Fortschr Rontgenstr Nuklearmed*, October, 1959, 91: 457–469. (*Universitätsklinik, Münster Westf., Germany)

A detailed description of 1 case, including presentation of 9 roentgenograms and 4 microscopic reproductions, is followed by a discussion of the general features of this disease. Primary lymphosarcoma of the lung arises from the lymphoid structures of the pulmonary parenchyma, grows expansively as an intralobar sarcomatous focus, and infiltrates diffusely into the interstitium of the lung. Roentgenographically it appears as a round opacity or diffuse clouding which remains confined to a lobe for a long time, similar to chronic pneumonia. Extensive alveolar compression may be associated with a reduction in the volume of the lobe. The tumor may infiltrate smaller bronchi, causing irregularities of the contours or obstruction. The proximal bronchi usually remain patent.—J. HAAPANEN

CHEMOTHERAPY

The Use of Amphotericin B in the Treatment of Coccidioidal Disease. W. WINN*. *Amer J Med*, October, 1959, 27: 617–635. (*Tulare-Kings Counties Hosp., Springville, Calif.)

Observations and conclusions are reported based on the use of amphotericin B in 9 cases of severe coccidioidal disease with impending or actual dissemination, 6 cases of coccidioidal meningitis, and 7 patients presenting miscellaneous coccidioidal disease. The latter included peripheral skin granulomas and abscesses, illustrate protective coverage during surgical procedures and, in 1 instance, prophylactic treatment to prevent possible dissemination of primary coccidioidal infection during pregnancy. As a result of these preliminary observations, amphotericin B would appear to be the first truly effective agent that has become available against coccidioidal disease. Its use, however, is not simple, and requires perseverance and cooperation of the patient in order to deliver sufficient dosage to maintain effective serum levels for a period of 2 to 3 months, or even longer in severe infections. The mild toxic effects which appear in most patients can be minimized by simple control measures. Unless this antimicrobial is used aggressively and with determination, serious forms of coccidioidomycosis will continue to result in a high mortality, which should no longer be acceptable.
—T. H. NOEHREN

Effect of Glucocorticoids on the Course of Tuberculous Exudative Pleurisy (in German). H. BRÜCKNER* and G. FIEGEL. *Tuberkulosearzt*, October, 1959, 13: 705–710. (*Martins-Krankenhaus, Koblenz, Germany)

Eighteen patients with tuberculous exudative pleurisy were treated with isoniazid and small doses of oral prednisone, combined at 6-day intervals with 2 to 3 intrapleural injections of the following combination: 60 mg. of prednisolone acetate (Deltacortril®), 1 gm. of streptomycin, and 250 mg. of a broad-spectrum antimicrobial. In all 18 cases, the absorption of the exudate occurred within 2 to 3 weeks and without formation of fibrous adhesions.—J. HAAPANEN

Isoniazid in Experimental Tuberculous Chancre of the Skin in the Guinea Pig (in Spanish). A. SAENZ* and J. SCANDROGLIO. *Hoja Tisiol*, June–September, 1959, 19: 105–112. (*Facultad de Medicina, Montevideo, Uruguay)

Isoniazid in a dosage of 2.5 mg. per kg. of body weight was used in the treatment of experimental tuberculous chancre of the skin in guinea pigs. The drug favored healing of the ulcer within a 30-day period, reducing the size of the satellite node, and preventing the development of visceral internal lesions. It also brought about a connective tissue neoformation and the early development of elements of cell metaplasia.—H. GARCÍA

Excretion of Pyruvic Acid Isonicotinoyl Hydrazone during Isoniazid Treatment (in Czech). M. KOHOUT* and R. KRULÍK. *Rozhl Tuberk*, January, 1959, 19: 65–68. (*Tuberculosis Research Institute, Prague, Czechoslovakia)

Following a peroral dose of 350 mg. of isoniazid, the urinary excretions of 52 patients were studied. It was found that the level of excreted pyruvic acid increased seven fold, of which 24 per cent was in the form of isonicotinoyl hydrazone.
—J. ILAVSKY

The Action of Small Doses of Isoniazid Given Intradermally in Experimental Tuberculosis. II. Late Behavior of Guinea Pigs and Their Resistance to a Second Experimental Infection (in (Italian). P. GUGLIELMETTI*, L. F. SIGNORINI, and G. FISSIMARRACINI. *Arch Tisiol*, August, 1959, 14: 782–794. (*Osp. Sanatoriale, Pratolino, Florence, Italy)

Four groups of guinea pigs were infected subcutaneously with 1 mg. of *M. tuberculosis* strain AM. The animals of 3 groups were daily inoculated intradermally with 2 mg. of isoniazid, starting either 1, 15, or 35 days after infection, while treatment was stopped simultaneously after 98

days. The fourth group served as a control. Two months later, some of the guinea pigs were killed, gross-examined, and portions of various organs were cultured in Petragnani's medium to detect the presence of tubercle bacilli. The remaining animals, with a new control group, were infected subcutaneously with 10 mg. of the same strain and allowed to live until they died spontaneously. The treatment with isoniazid protected the infected guinea pigs until at least 2 months after its interruption; when treatment was started early and maintained for 3 months, a complete biologic recovery resulted. A substantial resistance to the second large infection was shown only by the animals of the latter group, which were treated early after infection.—I. Archetti

Early Treatment of Pulmonary Tuberculosis with Kanamycin Combined with Thioamide (in Italian). G. Daddi*, M. Corda, C. Grassi, and C. Sacerdoti. *G Ital Tuberc*, September–October, 1959, 13: 267–273. (*U. of Milan, Italy)

Twenty patients with postprimary tuberculosis were treated for 2 months with kanamycin combined with thioamide in a daily dosage of 1 gm. Kanamycin was given to 1 group every third day, and thioamide in the intervening days; to a second group, both drugs were given every day. Fourteen patients were afterward treated with different combinations of various antimicrobials for a period of 60 days. Tolerance was generally good, and only light untoward symptoms were observed. All of the patients (save 1 with a serious bilateral lesion) improved both roentgenographically and clinically; 9 of 16 with sputum positive for *M. tuberculosis* became negative. Improvement was very good in 5 patients, moderate in 7, and minimal in the remaining 7.—I. Archetti

Macrocyclon in the Treatment of Pulmonary Tuberculosis. D. H. A. Boyd*, S. M. Stewart, A. R. Somner, J. W. Crofton, and R. J. W. Rees. *Tubercle*, October, 1959, 40: 369–376. (*National Institute for Med. Research, London, England)

Macrocyclon is the name given to the most active and least toxic of a series of non-ionic, surface-active polyoxyethylene ethers (detergents) with varying degrees of antituberculous activity. In this paper, the results are given of a pilot clinical trial of this agent which, in animals, appears to act through the host rather than by a direct attack on the tubercle bacillus.

No effect on the patients' clinical condition was observed and the positivity of the sputum for tubercle bacilli was not reduced. This failure is disappointing in view of the encouraging results of animal experiments. The most likely explanation for the differing effect of macrocyclon in animal and human tuberculosis is the differing role of the monocyte in the two diseases. If the therapeutic activity of macrocyclon is only effective on intracellular bacilli—and experimental studies strongly support this hypothesis—then, since intracellular bacilli are rare in chronic pulmonary tuberculosis in man, little or no activity would be expected.—M. J. Small

Restrictions Imposed on Antibiotic Therapy by Renal Failure. C. M. Kunin and M. Finland*. *AMA Arch Intern Med*, December, 1959, 104: 1030–1050. (*Boston City Hosp., Mass.)

Results of blood level determinations may serve as a useful guide to the need for restrictions on antimicrobial therapy imposed by renal failure. The size and frequency of doses which properly may be used in patients with impaired renal function depend largely upon the elimination rate constant and the apparent volume of distribution of the drugs. In patients with renal failure, the elimination rate constant of antimicrobials excreted largely by the kidneys is decreased, and the related "half-life" of the drugs in the blood is markedly prolonged. The exact change in these rate measurements produced by any given antimicrobial as a result of renal failure is best determined empirically for each drug. In general, the more rapidly a drug is cleared by the kidney, the more likely it is to appear in the urine at therapeutic levels (in spite of renal failure) when the levels in the blood are at the usually desired concentrations. Factors which influence the limitations imposed by renal failure are outlined and tabulated for streptomycin, penicillin, the tetracyclines, erythromycin, novobiocin, bacitracin, neomycin, kanamycin, polymyxin B, vancomycin, and ristocetin.—W. J. Steininger

Evaluation of Continuous Antibiotic Therapy in Chronic Bronchitis. J. McC. Murdoch*, W. J. N. Leckie, J. Downie, R. H. A. Swain, and J. C. Gould. *Brit Med J*, December 12, 1959, No. 5162: 1277–1285. (*U. of Edinburgh, Scotland)

Two double-blind trials of continuous daily tetracycline–oleandomycin and oxytetracycline treatment in patients with chronic bronchitis were carried out during the winters of 1957–1958 and 1958–1959, respectively. Twenty-three patients were observed in the first trial and 75, including 20 from the former, were seen in the second. The antimicrobial-treated groups were greatly benefited as compared with the groups receiving placebos. Improvement was judged on the basis of reduction in the number and severity of acute exacerbations, by eradication of *H. influenzae* and

pneumococcus from the sputum, and by statistical comparison of sickness in the treated as against the untreated groups. Serial sputum examinations were of value in the assessment of each patient's progress, but single specimens did not necessarily reflect the condition, since *H. influenzae* and pneumococcus were not isolated from every specimen. A significant rise in antibody titer to the influenza viruses was demonstrated in 14 patients during the second trial, but only 3 of them had clinical influenza. Subclinical infection in the remaining 11 did not obviously affect their bronchitis. Side effects were infrequent and not serious. Diarrhea was mildly troublesome in 15 of the 47 patients receiving antimicrobials. Gross disturbance of normal surface flora of the respiratory and intestinal tracts was not evident. Antimicrobial-resistant strains of coliform species and *S. aureus* occurred in some patients, mainly in those receiving antimicrobials, but were not significantly associated with clinical deterioration.

It was found practicable to manage patients on an outpatient or domiciliary basis. This had the advantages of a lower over-all cost than hospital treatment which, in any case, carries with it the attendant dangers of superinfection with drug-resistant and often highly virulent microorganisms. It is therefore preferable, should exacerbations of bronchitis arise, to treat them in the home rather than to seek immediate admission to hospital. It is concluded that continuous daily oxytetracycline therapy in advanced cases of chronic bronchitis, although apparently expensive, is less costly than the treatment of exacerbation of the disease in hospital. It is also safe and can be recommended as a reliable method of preventing such exacerbations (after authors' summary).—E. A. Riley

Treatment of Tuberculous Lymphadenitis (in Czech). D. Tlach*. *Rozhl Tuberk*, November, 1958, 18: 676–679. (*University Hosp., Brno-Bohunice, Czechoslovakia)

Twenty-five patients with peripheral tuberculous lymphadenitis were treated with a combination of antimicrobials (streptomycin, isoniazid, and PAS). The average time of hospitalization was 86 days. Antimicrobial therapy was then continued at various outpatient departments and dispensaries. Antimicrobial drugs were administered an average of 7.3 months. The results of treatment were evaluated 13 months later. In 14 patients, the lymph nodes were no longer palpable, in 6 they were substantially reduced. in 4 they remained unchanged; 1 patient died of generalized tuberculosis. If an enlarged lymph node does not improve during antimicrobial therapy, it should be surgically removed. —J. Ilavsky

Result of Treatment of Pneumoconiosis Complicated by Tuberculosis. J. H. R. Ramsey* and A. Pines. *Brit Med J*, September 5, 1959, No. 5148: 345–347. (*Edinburgh U., Scotland)

All of the cases of pneumoconiotuberculosis that were admitted into 3 Scottish hospitals from 1953 to 1958 have been analyzed. There were 25 patients, 18 of whom had progressive massive fibrosis. In all, except 1 who defaulted and another who relapsed temporarily, the sputum has become consistently negative. Twenty were treated initially with daily or intermittent streptomycin together with daily PAS and isoniazid. The remainder received combinations of 2 drugs. After conversion, outpatient treatment with PAS and isoniazid was given. The mean duration of chemotherapy has been 25 months. Although 8 patients are still continuing chemotherapy, in 4 this has been completed and, during a mean period of 8.9 months afterward, none has relapsed. Four have died from nontuberculous causes. There has been slight roentgenographic resolution in more than half of the patients, but cavity closure was obtained in only 1 of those with progressive massive fibrosis (Authors' summary in part). —E. A. Riley

Advances in Treatment of Chronic Pulmonary Tuberculosis in Children. S. J. Steel* and F. J. Bentley. *Tubercle*, October, 1959, 40: 377–383. (*High Wood Hosp. for Children, Brentwood, Essex, England)

An investigation has been made of the results in 147 children with chronic pulmonary tuberculosis treated at High Wood Hospital. Seventy-two patients were treated during 1947 and 1948, and 67 of these were followed up for 10 years; 75 were treated during 1954, and 71 of these were followed up for at least 3 years. In 1947–1948, all of the children were treated by graduated rest without any chemotherapy, and all but 6 received collapse therapy. In 1954, all of the children received chemotherapy; 38 had collapse therapy, 8 underwent radical surgical treatment, and 25 were treated with chemotherapy alone.

Of 67 children in the 1947–1948 group, 7 died in hospital and another 8 died within 3 years of discharge. In addition, 14 relapsed and 2 others gradually deteriorated. The mortality rate would probably have been higher but for treatment of relapses with chemotherapy. Of 71 patients in 1954 (including 16 with extensive lesions), there were no deaths either in hospital or during the 3-year follow-up period, and only 2 patients, both

with minimal lesions, relapsed. The results were satisfactory in 25 patients who were treated with chemotherapy alone and compared well with those patients treated with both chemotherapy and artificial pneumothorax. Although chemotherapy is shown to have reduced the incidence of complications in children treated with artificial pneumothorax, this latter form of treatment has now been abandoned. Surgical treatment is preferably confined to resection for gross residual disease, unclosed cavities, or when resistant organisms prevent effective chemotherapy. The management of the minimal case has been simplified by the introduction of chemotherapy, and it is pointed out that all patients with lesions not obviously old and healed—however small—should receive early treatment with antituberculosis drugs.
—M. J. SMALL

*The Medical Letter**, April 1, 1960, 2: 25–28. (*136 E. 57 St., N. Y., N. Y.)

Chemotherapy of malignant lymphomas: nitrogen mustard (Mustargen Hydrochloride®), triethylene melamine (TEM®), triethylene thiophosphoramide (Thio-TEPA®), chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®), and the corticosteroid hormones. Effects of meals on absorption of oral anti-infective agents. A conjugated equine estrogen (Premarin®) for control of bleeding.

The Medical Letter, April 15, 1960, 2: 29–32.

Vasopressors in the relief of shock: norepinephrine (Levophed®) and metaraminol (Aramine®). Phenmetrazine (Preludin®), a sympathomimetic-amine appetite depressant pharmacologically similar to the amphetamines; and dextroamphetamine. Homagenets® ("the only homogenized vitamins in solid form") and vitamin absorption.

PULMONARY PHYSIOLOGY

Pulmonary Transcapillary Exchange of Na^{24} and P^{32}-Labelled Phosphate in Pulmonary Emphysema. M. A. ROTHSCHILD*, A. L. DAVIS, M. ORATZ, and S. S. SCHREIBER. *J Clin Invest*, December, 1959, 38: 2224–2228. (V. A. Hosp., New York, N. Y.)

The pulmonary transcapillary exchange of Na^{24}- and P^{32}-labeled phosphate was determined in 17 control subjects and in 13 patients with pulmonary emphysema. Exchange of both ions is markedly reduced or practically abolished in emphysema. Factors causing this diminished transfer are discussed.—E. DUNNER

Blood Ammonia in Chronic Pulmonary Emphysema. R. DUTTON*, W. NICHOLAS, C. J. FISHER, and A. D. RENZETTI, JR. *New Engl J Med*, December 17, 1959, 261: 1369–1373. (*Johns Hopkins Hosp., Baltimore, Md.)

Seventeen of 34 patients with chronic pulmonary emphysema without congestive heart failure or clinical evidence of liver disease were found to have abnormal blood ammonia concentrations. Pulmonary function studies carried out in 12 of these 34 patients indicated that, in general, the blood ammonia was more likely to be elevated in those with the more severe respiratory physiologic defects. It is suggested that chronic severe arterial hypoxia may interfere with the capacity of the liver to metabolize ammonia. A positive correlation was noted between the minute volume of ventilation at rest and the calculated arterial ammonia tension. Although it is well recognized that the respiratory centers of patients with chronic carbon dioxide retention are relatively insensitive to this gas, and that arterial hypoxia is playing an important part as a respiratory stimulus in such situations, the possibility that ammonia is an additional respiratory stimulant cannot be excluded. Further investigation of this possible action of ammonia is warranted.
—M. J. SMALL

A Simple Apparatus for the Detection of Obstructive Pulmonary Emphysema and Other Conditions of Diffuse Bronchiolar Obstruction. K. A. J. JÄRVINEN*. *Ann Med Intern Fenn*, Fasc. 4, 1959, 48: 219–229. (*Institute of Occupational Health, Helsinki, Finland)

A simple apparatus is presented for the detection of diffuse bronchiolar obstruction. The concept of this apparatus developed from the observation that a person suffering from bronchiolar obstruction when breathing through a capillary tube is more capable of expiration than of inspiration—a phenomenon which is paradoxical when compared with the respiration of such a person breathing naturally. The apparatus is composed of 2 oxygen flow meters (1 for inspiration and 1 for expiration) to which are attached similar capillary tubes for resistance. By use of the apparatus, 72 individuals suffering from bronchiolar dyspnea (45 with obstructive pulmonary emphysema and 27 with bronchial asthma) were distinguished from 155 healthy controls. Furthermore, a sharp difference was observable in regard to certain groups of diseases which may in practice be confused with bronchiolar obstruction owing to their common symptom of obstruction. The results obtained with the flow-meter apparatus correspond well with those obtained in pulmo-

nary function tests. The greatest practical significance of the apparatus is in the diagnosis of obstructive pulmonary emphysema.—E. DUNNER

The Respiratory Effects of Progesterone in Severe Pulmonary Emphysema. J. CULLEN*, V. BRUM, and W. REIDT. *Amer J Med*, October, 1959, 27: 551–557. (*V. A. Hosp., Albany, N. Y.)

Daily administration of intramuscular progesterone in oil produced an increase in both the total ventilation and alveolar ventilation in 7 patients with severe pulmonary emphysema, and in 2 normal subjects. This hyperventilatory effect of progesterone was accompanied by a significant fall in carbon dioxide tension in only 3 of the 7 emphysematous patients studied. It seems that the alveolar ventilation must show a greater percentage increase than the total ventilation in order that the carbon dioxide tension be reduced. In 3 of the 7 emphysematous patients studied, the increased ventilation was associated with an increased oxygen consumption. It is believed that this increased oxygen consumption was due to increased work of breathing as a result of hyperventilation. There was no evidence of a bronchodilator effect of progesterone. Although the ventilatory response to carbon dioxide inhalation demonstrated a lower threshold to carbon dioxide during progesterone therapy, the evidence was inconclusive as to whether progesterone actually increased the sensitivity of the respiratory center. The one emphysematous patient studied showed less of a response to carbon dioxide inhalation than the normal subjects. This diminished response was not believed to indicate necessarily a decreased sensitivity of the respiratory center, as it may have been due to both the fact that his oxygen consumption doubled and that his total ventilation approached his maximal breathing capacity (after authors' summary).
—T. H. NOEHREN

Cases of Fallot's Tetralogy with Late Cyanosis (in Turkish). C. ABAOGLU*, R. BERKMEN, A. TASCI, and S. YILMAZ. *Tuberk Toraks*, September–December, 1959, 7: 117–130. (*U. of Istanbul, Turkey)

Two cases are presented of Fallot's tetralogy with late manifestation of cyanosis. These 2 cases are the 15th and 16th atypical, noncyanotic cases to be reported in the world literature. The first case had manifest cyanosis only immediately after birth and at the age of 25. Diagnosis was confirmed by autopsy. A high, small interventricular defect was found together with a larger opening of the aorta into the left ventricle than to the right. The presence of diastolic murmur and complete arrythmia at the terminal stage, as well as systolic murmur, are the first such physical signs detected in such cases. The second case had no cyanosis manifest at the age of 14. Diagnosis was made by cardiac catheterization, and left-to-right shunt was found which was believed to prevent the manifestation of cyanosis.—S. SOLU

Studies on Respiratory Mechanics and the Work of Breathing in Pulmonary Fibrosis. J. WEST* and J. ALEXANDER. *Amer J Med*, October, 1959, 27: 529–544. (*Presbyterian Hosp., N. Y., N. Y.)

In vivo measurements have indicated considerable alteration in the physical properties of the lungs involved by infiltrative or fibrotic changes of various etiology. Studies in 9 patients with such involvement revealed a marked reduction in pulmonary compliance as compared to the normal. Altered compliance was better correlated with reduction in total lung capacity than with abnormality in gas exchange, suggesting that changes in the interstitial tissues at wider planes are more important than those in the alveolar capillary membrane in determining the elastic behavior of the fibrotic lung. The limit of distensibility in the fibrotic lung was reached at a very small volume, and further inspiratory expansion of the chest did not occur, although these patients were capable of developing a negative intrathoracic pressure equal to or greater than the normal. Resistance to air flow and tissue deformation differed little from the normal in most cases, so that the pressure volume loop described by the fibrotic lung during the inspiratory capacity maneuver assumed a sickled configuration which was quite characteristic. In the patients with pulmonary fibrosis, intrathoracic pressure at end-expiration was less negative than normal and equivalent to atmospheric pressure in most, suggesting that the fibrotic lung had lost the normal elastic retractile force at the volume corresponding to the functional residual capacity.

The elastic behavior of the fibrotic and emphysematous lungs are compared. In the emphysematous lung there is little change in total capacity relative to the normal but, because of loss of elasticity, the lung may be expanded to its total capacity by a transpulmonary pressure as little as ½ that required for the normal lung. In the fibrotic lung there is marked reduction in lung volume, and inflation to total capacity may necessitate a transpulmonary pressure twice the normal. Augmented elastic resistance of the fibrotic lung resulted in an abnormally high respiratory work expenditure per unit volume of inflation and, therefore, per liter of ventilation over a wide range of respiratory rates. The com-

bined effects of hyperventilation and greater work per liter of ventilation made for a striking increase in the estimated work of breathing in these patients, both at rest and during exercise (Authors' summary).—T. H. NOEHREN

Static Volume-Pressure Relations of Excised Lungs of Infants with Hyaline Membrane Disease, Newborn and Stillborn Infants. I. GRIBETZ*, N. R. FRANK, and M. E. AVERY. *J Clin Invest*, December, 1959, 38: 2168–2175. (*Harvard School of Public Health, Boston, Mass.)

Comparison was made of virtually static volume-pressure relations of excised lungs obtained from 10 infants with hyaline membrane disease, 5 newborns dying from other causes, and 5 stillborn infants. To eliminate the influence of size on these measurements, volume was expressed as milliliters of gas per gram of tissue. Special emphasis was given to the volume-pressure relations during deflation from a peak airway pressure of 35 cm. H_2O. At all pressures the lungs with hyaline membranes contained less gas per unit of weight than the control lungs; in addition, the slope of their entire volume-pressure curve was depressed. The low compliance in membrane-containing lungs was thought to be due to a reduction in number of units participating in ventilation. The relative importance of changes in surface forces that might lead either to a collapse of units or to increased resistance to inflationary pressures and mechanical plugging could not be determined from these studies.—E. DUNNER

Syndrome of Extreme Obesity and Hypoventilation: Studies of Etiology. J. HACKNEY*, M. CRANE, C. COLLIER, S. ROKAW, and D. GRIGGS. *Ann Intern Med*, September, 1959, 51: 541–552. (*College of Medical Evangelists, Los Angeles, Calif.)

The results of cardiopulmonary studies on 17 patients with the syndrome of extreme obesity and hypoventilation implicate excessive breathing work as a cause of the hypoventilation and associated features. An attempt to duplicate some of the functional abnormalities of these patients was made by binding the chests and abdomens of 10 control subjects. Pulmonary function studies were abnormal during binding, and these functional changes were similar to those of the obese syndrome patients (Author's summary).
—T. H. NOEHREN

Apneic Oxygenation in Man. M. J. FRUMIN*, R. EPSTEIN, and G. COHEN. *Anesthesiology*, November–December, 1959, 20: 789–798. (*College of Physicians and Surgeons, Columbia U., N. Y., N. Y.)

Apneic oxygenation or "diffuse respiration" deals with prolonged suppression of respiratory function in man while full oxygenation and other vital functions are maintained. The study was prompted by the widespread interest in respiratory acidosis during anesthesia and surgery. The method is described in detail. Apneic oxygenation was carried out in 8 essentially healthy patients for periods of 15 to 55 minutes. In apneic oxygenation, only a small fraction of metabolically produced carbon dioxide enters the alveoli even though carbon dioxide production may equal the oxygen consumption in the metabolizing tissues. A reduction of barometric pressure in the alveoli occurs which tends to move gas from the outside down to the alveoli. The volume of such gas moving down the trachea has been measured.

The observations made are used to define the limits of applicability of the results to man. Moderate to severe arterial hypertension followed by mild hypotension occur when artificial respiration is resumed. A discussion is given on the relationship of this hypertension and the increases in plasma sodium, potassium, epinephrine, and norepinephrine concentrations during apnea. Arrhythmias were found only once. Severe metabolic acidosis accompanied the respiratory acidosis.
—E. SHABART

Total Anomalous Pulmonary Venous Return: Infradiaphragmatic Type, Clinical Manifestations. B. SMITH*, T. R. FRYE, and W. A. NEWTON, JR. *AMA J Dis Child*, November, 1959, 98: 642–643. (* Children's Hosp., Columbus, Ohio)

The present study is an analysis of the clinicopathologic features of the 2 main varieties of anomalous pulmonary venous return: supra- and infradiaphragmatic. This anomaly, with the pulmonary veins draining into the inferior vena cava or portal vein, was encountered in 9 cases of 22 autopsied between 1952–58, but in only 5 was it present as an isolated anomaly. The supra- and infradiaphragmatic varieties of total anomalous pulmonary venous return are two strikingly different entities in their clinical manifestations. With 1 exception, the 21 cases reported to date have been diagnosed at autopsy. There is sufficient evidence accumulated from previous reports by other authors, plus the 5 cases here analyzed, to substantiate the following diagnostic criteria for suspicion of total anomalous pulmonary venous

return, infradiaphragmatic variety: newborns with deep cyanosis and severe dyspnea, showing on chest roentgenogram a normal-size heart and a typical diffuse mottling of the lungs. The chest roentgenogram showed, in all cases, a marked increase of pulmonary vasculature appearing as a fine, diffuse, granulated mottling of the lung parenchyma. This is in clear contrast with the supradiaphragmatic variety, for which the pathognomonic roentgenographic appearance of the enlarged heart greatly facilitates the diagnosis.
—M. J. SMALL

The Use of Spirographic Methods for Early Diagnosis of Respiratory Disturbances in Athletes (in Czech). Z. HORNOF* and V. NOVOTNÝ. *Cas Lek Cesk*, January 23, 1959, 98: 113–115. (*University, Plzeň, Czechoslovakia)

Repeated tests were performed on 120 leading Czechoslovak athletes. The clinical and spirometric results in most cases, but not always, were in complete agreement. In the majority of cases in which some deviations were found during clinical tests, spirometric results confirmed them. However, there were also cases in which clinical tests gave normal results and the spirometric examination uncovered hidden defects of respiration. Two such persons were analyzed and their fitness for athletic competition is discussed.
—J. ILAVSKY

Spirometric Examination Following Bilateral Resection (in Czech). L. FURY*, V. HLADIL, J. KROPÁČEK, and J. NECHVÁTAL. *Rozhl Tuberk*, November, 1958, 18: 642–646. (*Masaryk U., Brno, Czechslovakia)

Spirometric examinations were performed in 9 patients before operation, after the first operation, and after the second operation. It was found that, following unilateral resection, the other lung partially compensates for the functional loss. After the second operation, the compensation is minimal, because the other lung is already functionally inferior.—J. ILAVSKY

The Carbon Dioxide Spirometer: A New Instrument for the Rapid Evaluation of the Circulation. J. J. OSBORN*. *AMA J Dis Child*, November, 1959, 98: 625–626. (* Stanford U. Hospitals, Calif.)

Respiratory air flow is routinely measured by recording the differential pressure across a low-resistance screen while a subject breathes through it. Respiratory carbon dioxide concentration can be accurately recorded by sampling continuously through a rapid-response infrared detector. If the respiratory flow curve is continuously multiplied by the carbon dioxide concentration curve (with a suitable delay circuit to bring the two exactly into phase), the resulting curve represents carbon dioxide flow. Both of these flow curves can be simultaneously electrically integrated into volume curves. The carbon dioxide spirometer consists of suitable sensing devices, an 8-channel recorder, and an analogue computer with an adjustable time delay with suitable multiplying and integrating circuits to perform these operations and record the results. In addition to flows and volumes of both air and carbon dioxide, it can record carbon dioxide vital capacity, single-breath carbon dioxide excretion curves, et cetera.
—M. J. SMALL

Pulmonary Ventilation. Blood Flow Relationships in Interstitial Disease of the Lungs. J. READ* and R. WILLIAMS. *Amer J Med*, October, 1959, 27: 545–550. (* Medical School of London, England)

Pulmonary ventilation and blood flow relationships have been studied in 17 subjects with apparently pure interstitial disease of the lungs, and in 11 subjects with interstitial disease complicated by cyst formation or probable emphysema. Subjects with apparently pure interstitial disease frequently had markedly uneven ventilation of the lungs which, in the presence of uniform blood flow, led to marked ventilation-perfusion imbalance. In subjects with complicated interstitial disease, abnormalities of pulmonary blood flow, not found in those with pure interstitial disease, were common (Authors' summary).
—T. H. NOEHREN

MICROBIOLOGY AND IMMUNOLOGY

A Newly-isolated Strain of Mycobacteria Nonpathogenic for the Guinea Pig and Possessing Special Metabolic Characteristics (in Italian). M. MORELLINI* and S. FERRARI. *Ann Ist Forlanini*, No. 2, 1959, 19: 175–186. (* Instituto C. Forlanini, U. of Rome, Italia)

A strain of mycobacteria nonpathogenic for the guinea pig, whose colonies on Petragnani medium had the macroscopic appearance of those obtained with tubercle bacilli, was isolated from an indicator tincture (litmus tincture), used in the laboratory as a reagent. Both the Desbordes and the Middlebrook-Dubos tests for virulence and inoculation into guinea pigs were negative. The strain belongs to the so-called paratuberculous group: it is resistant to PAS, streptomycin, and isoniazid, and has a relative susceptibility to carbomycin. The growth-curve study showed that

its nutritional requirements were completely fulfilled by the indicator tincture, even in a 1.5 per cent aqueous solution: the main growth factor in the tincture should be azolitmin, a nitrogen-containing substance.—I. ARCHETTI

Catalase Activity of Isoniazid-resistant Tubercle Bacilli (in Spanish). A. SAENZ*. *Hoja Tisiol*, June–September, 1959, 19: 129–134. (* Facultad de Medicina, Montevideo, Uruguay)

Middlebrook's technique was used to determine the catalase activity in 130 strains of tubercle bacilli. There was no direct or absolute correlation between the degree of resistance and the catalase activity; 8.5 per cent of the strongly isoniazid-resistant strains proved to be catalase positive. —H. GARCÍA

High-pressure Chamber for Culture of *M. Tuberculosis* at Pressures of 200–400 Atmospheres (in Czech). L. ŠULA*, J. ŠULOVÁ, and J. KUBÍČEK. *Rozhl Tuberk*, January, 1959, 19: 33–37. (* Tuberculosis Research Institute, Prague, Czechoslovakia)

A simple apparatus for high-pressure cultures was used in these studies. It consists of the pressure chamber filled with oil and the culture chamber filled with glycerol. The inoculated broth in a sealed polyethylene tube is inserted in the culture chamber and the desirable pressure is produced by a screw pressing a piston into the pressure chamber. The pressure is transmitted into the culture chamber, which is made of an elastic polyamid sheet. The whole apparatus measures 2½ x 20 inches. When the strain SAPC (Souche Homogene Arloing Paul Courmont) was grown at the pressure of 200 atmospheres per square cm., cord formation occurred which was never observed under normal culture conditions. Acid-fast filaments resembling actinomycetes were observed when this high pressure culture was transferred into broth and grown under normal pressure. These findings suggest that high pressure considerably influenced cell division without influencing its growth. Such modified mycobacteria may have interesting properties. The experiments are being continued.—J. ILAVSKY

The Influence of Galvanic Current upon the Growth of *M. Tuberculosis* (in Czech). J. SALZMANN* and O. KULA. *Rozhl Tuberk*, December, 1958, 18: 773–777. (* Sanatorium, Nová Polianka, Czechoslovakia)

The action of electric current upon the growth of *M. tuberculosis* was studied. Smears of positive sputum were tested using the slide culture method in Šula medium. The effects of galvanic current alone and in combination with antituberculosis drugs were followed and compared. It was found that electric current alone does not inhibit growth of mycobacteria, but causes striking morphologic changes. Marked inhibition of growth was observed when the electric current was applied simultaneously with antituberculosis drugs. There was no demonstrable difference between the growth near the anode or the cathode. —J. ILAVSKY

Positive Cultures of *M. Tuberculosis* Found in So-called Clinical Material (in Czech). R. VIHAN*. *Rozhl Tuberk*, November, 1958, 18: 683–686. (* Hygienic-Epidemiologic Station, Prague, Czechoslovakia)

At the Department of Microbiology of the Regional Institute of Hygiene and Epidemiology in Prague, all samples submitted for bacteriologic examination are tested for *M. tuberculosis* regardless of the clinical diagnosis. Positive tuberculous cultures were found in an average of 2.5 per cent of the tested samples, and 130 to 146 new and previously undiagnosed cases of tuberculosis a year were detected.—J. ILAVSKY

EXPERIMENTAL PATHOLOGY

Study of the Toxicity of Dust with Use of the *In Vitro* Dehydrogenase Technique. J. MARKS* and G. NAGELSCHMIDT. *AMA Arch Industr Health*, November, 1959, 20: 383–389. (*Public Health Laboratory Service, Cardiff, Wales)

Macrophages were incubated with dust, and their capacity to reduce tetrazolium (dehydrogenase activity) was measured. The quantity of dust which reduced the activity of a standard cell culture by 50 per cent was called the toxic dose. A comparison was made between the toxic doses of various types of dust and previous observations on the fibrogenic activity of the same or similar dusts made in intact animals. With certain qualifications, good correspondence was found between the two techniques. On the basis of the results obtained, a hypothesis is advanced concerning the mechanism of the biologic effects of silica dust (Authors' summary).—T. H. NOEHREN

An Early Inflammatory Skin Lesion Induced in Guinea Pigs with PPD. H. C. MANSMANN, JR.* *AMA J Dis Child*, November, 1959, 98: 620. (*U. of Pittsburgh, Penn.)

As the Arthus reaction depends upon precipitating antibodies against the specific antigen, a histologic study was undertaken on the 4-hour skin reactions observed in actively immunized guinea pigs with PPD or unheated tuberculoprotein. The skin lesions elicited with PPD and unheated tuberculoprotein in the 2 groups of guinea pigs were similar both grossly and histo-

logically to mild Arthus reactions. However, 100 γ of PPD were necessary to produce the same size lesions as did 10 γ of unheated tuberculoprotein. Serum from these guinea pigs was studied by the Preer agar-diffusion method for the presence of precipitating antibodies. Positive results were obtained only when unheated tuberculoprotein was added to the serum from animals that were immunized with unheated tuberculoprotein.—M. J. SMALL

Changes in the Lipid Spectrum of the Lungs and Kidneys following High Experimental Doses of Salicylates (in Slovak). T. R. NIEDERLAND*, P. KOVACS, and R. DZÚRIK. *Brat Lek Listy*, August 15, 1958, 38-11: 137–144. (*Komenský U., Bratislava, Czechoslovakia)

In previous experiments it was established and recently reported that, following large doses of salicylates, there are substantial changes in rabbit livers characterized by: (*1*) a sudden lowering of the glycogen level, and (*2*) changes in the lipid fractions. In another study, it was found that in partially nephrectomized rats it is difficult to cause a fatty infiltration of the liver. On the basis of these observations, new groups of experiments were undertaken and the role of the kidneys and lungs in the metabolism of fat was studied.

In the first group, an extreme form of experimental arrangement, 13 experimental and 13 control rabbits were used. A total dosage of 0.69 gm. of sodium salicylate per kg. per day was administered subcutaneously in a 10 per cent solution divided into 3 doses. Following the salicylate administration, there was a statistically significant drop of the lipid phosphorus values in both lungs and kidneys. Fatty-acid esters remained unchanged in lungs and significantly decreased in kidneys.

In the second group of experiments, 10 experimental and 11 control rabbits were used. Twice a day, 0.81 gm. of sodium salicylate per kg. per day in 10 per cent solution was injected subcutaneously. Levels of fatty acids and of lipid phosphorus in the lungs remained unchanged, while the cholesterol values significantly decreased. No significant changes were found in the kidneys. No significant changes were present in the serum levels of the lipidic fractions.—J. ILAVSKY

Experimental Silicosis: The Inhibitory Effect of Iron. P. GROSS*, M. WESTRICK, and J. MCNERNEY. *Dis Chest*, January, 1960, 37: 35–41. (*Mellon Institute, Pittsburgh, Penn.)

In 1932 it was shown that when quartz particles are coated with iron their fibrogenic action is inhibited. Later, Gardner concluded that no inhibition could occur unless the inhibiting substance were within the same macrophage as the quartz particle it inhibited. This paper states that the production of experimental silicosis had been inhibited by iron and describes findings which appear to be at variance with Gardner's conclusion concerning this inhibition: that is, descriptions are presented of foci in experimental animals in which there was manifest inhibition of collagen formation in spite of the fact that abundant iron-free silica was demonstrable in such regions.—E. A. ROUFF

Modifications of Experimental Tuberculosis in the Guinea Pig Induced by Silica and Hyaluronidase (in Italian). V. GIULIANO*, L. LUCANIA, and L. PECCHIAI. *Ann Med Sondalo*, July–August, 1959, 7: 211–222. (*Ist. Anatomia Patologica, U. of Milan, Italy)

The purpose of this investigation was to study the influence of silica and hyaluronidase upon experimental tuberculosis in the guinea pig. Each of 4 groups of 6 guinea pigs was inoculated subcutaneously with *M. tuberculosis* strain H37Rv. In addition, the animals of 1 group each received, at the same time and by the same injection, hyaluronidase, silica, and both substances together; the fourth group acted as a control. All of the guinea pigs were killed 23 days after infection, and gross anatomic, histologic, and histochemical studies were performed in all of the animals. The results indicate clearly that both hyaluronidase and silica worsened the evolution of the infection, but no summation of effects was shown. The mechanism of influence was different, as demonstrated macro- and microscopically: the main reason for this difference could be due to the various properties of the two substances, hyaluronidase being a diffusion factor, and silica a material which gives a characteristic hyperplastic reaction.—I. ARCHETTI

PUBLIC HEALTH AND EPIDEMIOLOGY

A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India. TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS. *Bull WHO*, 1959, 21: 51–144.

A 12-month controlled study comparing the merits of home treatment with those of sanatorium treatment for pulmonary tuberculosis was carried out at the Tuberculosis Chemotherapy Centre at Madras. One hundred and ninety-three patients were assigned to home or sanatorium treatment at random. Chemotherapy in both groups consisted of 200 mg. of isoniazid and 10 gm. of sodium PAS, given together in 2 doses. In spite of random allocation, the home series had more cases of serious disease, particularly in the female group. More irregularity in self-administration of drugs was

found in the home-patient group, particularly among females. The diet received by home patients was clearly inferior to the one consumed by sanatorium patients. Roentgenographic improvement was equally good in both groups. As for bacteriologic changes, the female patients treated at the sanatorium showed somewhat better results after 1 year than did those treated at home, while there was no difference in male patients. The overall results of domiciliary treatment sufficiently paralleled those of sanatorium treatment to recommend home treatment for the majority of patients in India.—H. Abeles

Preliminary Experience with Interrupted Sanatorium Treatment (in Czech). J. Petrus* and B. Urbančík. *Rozhl Tuberk*, November, 1958, 18: 664–669. (*Tuberculosis Hosp., Jablunkov, Czechoslovakia)

Shortage of hospital beds for tuberculous patients is a chronic problem in the Czechoslovak antituberculosis campaign. For that reason, the possibility of interrupted sanatorium treatment was tried and the following conclusions were reached. Disciplined patients can be temporarily discharged after about 6 months of treatment in the hospital. Ambulatory treatment must continue. Two to 3 months later they are readmitted for a control examination and the subsequent therapeutic procedure is decided. Satisfactory results can be obtained by this method if correct attention is given to the clinical picture as well as to the character of the patient. There were poor results in patients who insisted on the interrupted treatment in spite of unstabilized tuberculous processes. On the other hand, the interrupted treatment has a very favorable psychologic effect upon patients, reduces the number of days spent in the sanatorium, and enables more economical use of hospital beds and facilities.—J. Ilavsky

Persistence of Tuberculin Hypersensitivity after Vaccination (in Czech). Z. Nejedlá* and L. Hromádková. *Rozhl Tuberk*, November, 1958, 18: 670–675. (*Institute for Mothers and Children, Prague, Czechoslovakia)

A group of children were vaccinated with M-vaccine, prepared from *M. tuberculosis* var. *murinus Wells*. Tuberculin hypersensitivity was tested 8 weeks after vaccination using the Monrad test method. Children with positive reactions were repeatedly tested at 1- and 6-year intervals. It was found that, after 6 years, tuberculin hypersensitivity was present in 97 per cent. Those children who were tested with tuberculin every year had a higher percentage of positive reactions than the group tested only twice. This phenomenon occurred in children 4 years old and older. —J. Ilavsky

BCG Vaccination in Czechoslovakia (in Czech). V. Vojtek*. *Rozhl Tuberk*, January, 1959, 19: 18–25. (*Tuberculous Sanatorium for Children, Šumperk, Czechoslovakia)

Data compiled from all tuberculosis sanatoriums for children in Czechoslovakia show that 10,261 were treated for tuberculosis in the period 1954–1956. These children belong to the group already tuberculin-positive when BCG vaccination was contemplated. During the years 1948 to 1952, there were very insufficient vaccination rates. As a result, among the children born in that period there is a much higher incidence of tuberculosis than among children born during the years 1954 to 1957. Analysis of 898 cases of tuberculous meningitis show that 953 cases (94.3 per cent) were among nonvaccinated children, and the remaining 55 were not sufficiently checked for the results of vaccination. Under the present epidemiologic conditions, vaccination of all newborns seems to be the most reliable method.—J. Ilavsky

Comments on the Drive against Tuberculosis in Czechoslovakia (in Czech). R. Křivinka*. *Cas Lek Cesk*, October 17, 1958, 97: 1313–1316. (*Ministry of Health, Prague, Czechoslovakia)

In spite of all progress, the incidence of tuberculosis in Czechoslovakia is still high. The work of regional tuberculosis dispensaries will remain basic for antituberculosis campaigns. Departments of tuberculosis were organized in all districts of the state and are parts of the system of polyclinics. The district phthisiologist should be not only a good diagnostician and therapeutist, but a good organizer as well. He and all member workers of the polyclinics have to work not only in the health center, but they have to go and visit tuberculous patients in their homes and set up necessary arrangements right there. To isolate all sources of infection is ideal, but it is not possible from the practical viewpoint. For that reason it will be necessary to isolate first those patients who are most dangerous from the epidemiologic standpoint. All of these people have to be hospitalized as soon as possible without waiting weeks or months for admission to hospital.

BCG vaccination will remain the main tool of the preventive measures. Antituberculosis drugs must be used more extensively and surgical methods must be applied more often. Insufficient activity of surgeons in certain sanatoriums is one of the reasons why, in spite of prolonged hospitalization, positive sputum and cavities remain in very many patients. Most patients gladly and

voluntarily undergo hospitalization and treatment, but there are a few, mostly asocials and alcoholics, who have poor living conditions and for whom treatment must be enforced. For these problem patients, it will be necessary to organize forced detention departments in which treatment for alcoholism can also be administered. Rehabilitation of tuberculous patients and their reinstatement in industry is another problem requiring better understanding of all concerned.
—J. Ilavsky

Influence of Pulmonary Tuberculosis on Marriage (in Slovak). F. Pavlovič*. *Rozhl Tuberk*, December, 1958, 18: 797–799. (*Sanatorium, Tatranská Polianka, Czechoslovakia)

In an effort to investigate the influence of pulmonary tuberculosis on marriage, the author sent questionnaires to 1,034 former single male and female patients of the Sanatorium in Tatranska Polianka: 514 of the returned questionnaires were satisfactory for evaluation; 311 were from men, and 203 from women. Twenty-six per cent got married within 54 months after leaving the Sanatorium. Most of the men got married within 6 months, and most of the women within 13–18 months. One-fourth of the men married tuberculous women, and half of the women married men with pulmonary tuberculosis. Children were born to 51 per cent of the male patients and 42 per cent of the female patients. All of the children, with the exception of 5, were vaccinated against tuberculosis, and all of the children—with only 1 exception—are in good health. The great majority of those polled are happy in their marriages.
—J. Ilavsky

Training of Tuberculous Patients for Work in Health Services (in Slovak) A. Krchnavý* and J. Hejný. *Rozhl Tuberk*, December, 1958, 18: 790–796. (*Sanatorium, Vyšné Hágy, Czechoslovakia)

One hundred and fifty-two tuberculous patients were trained for work as nurses and laboratory assistants. All were chronic tuberculous patients of 4 or more years duration; 48 were teachers, 26 professionals, and 48 had never worked before. During the training course, health conditions improved in 38, remained unchanged in 108, and deteriorated in 6 patients. Immediately after completion of the training course, 122 participants were able to work; 26 others were able to work 1 year later, and only 4 remained permanently unfit for work. The authors conclude that training these tuberculous patients proved favorable and successful from the humane aspect, as well as medically, socially, and economically.
—J. Ilavsky

Tuberculosis in Professionals (in Slovak). M. Nosál*. *Lek Obzor*, January, 1959, 8: 28–33. (*Komenský U., Bratislava, Czechoslovakia)

The number of reported cases of tuberculosis in professionals has been increasing during the last few years, but not all of these cases are professional in origin. In many instances the professional origin is not only dubious, but quite impossible. The author, therefore, recommends the following 3 points be used as a basis for the diagnosis of tuberculosis as a "professional" disease for practical purposes: (*1*) proof of real exposure to tuberculosis infection, (*2*) proof of full health before exposure to infection, and (*3*) the precise beginning of the illness and a description of its development. However, even under these conditions there can be "nonprofessional" cases among health personnel, i.e., a sick member of the family can be a source of infection.—J. Ilavsky

A Bacteriological Irritation Analogue for Aerosols. A. Goetz* and N. Tsuneishi. *AMA Arch Industr Health*, August, 1959, 20: 167–180. (*California Institute of Technology, Pasadena)

The bacteriologic irritation analogue (BIA) test—as developed at present—is able to indicate qualitatively and to some extent quantitatively the irritation intensity of aerosols (smog, tobacco smoke, formaldehyde aerosols). It has been used in synthetic aerosols as an indicator for the degree of association of the irritant gas (formaldehyde) with air-borne particulate matter by comparative tests prior to and after passage through the aerosol spectrometer. The findings support the assumption that a fraction of the irritant gas molecules associates with the particle surface, and that this association produces an intensifying (synergistic) effect which increases with the aerosol concentration.—T. H. Noehren

Significance of Respiratory Symptoms and the Diagnosis of Chronic Bronchitis in a Working Population. C. M. Fletcher*, C. P. Elmes, A. S. Fairbairn, and C. H. Wood. *Brit Med J*, August 29, 1959, No. 5147: 266–275. (*Postgraduate Med. School of London, England)

Post Office employees in London (192 males and 192 females) aged 40 to 59 were studied by a symptomatic questionnaire, by measurements of sputum volume and ventilatory capacity, and by inspection of sickness absence records. The men had more cough and sputum than the women, but the prevalence of other symptoms and of chest illnesses was similar in the two sexes. Symptoms increased with age in the men but not in the women. These differences were only partly attributable to differences in smoking habits. The severity of phlegm production was graded ac-

cording to whether it occurred throughout the day, and this grading correlated well with the volume of sputum produced in the first hour after waking. Whether the phlegm was said to be perennial appeared not to matter. Ventilatory capacity was significantly impaired in the men, but not in the women, who had the higher grade of phlegm production, frequent wheezing, susceptibility to adverse weather, and a history of chest illnesses with an increase of phlegm production.

It is suggested that chronic bronchitis should be diagnosed in subjects with a productive cough not due to other causes, and that it should be graded in severity either according to the persistence of the symptoms throughout the day or according to the volume of sputum expectorated. Disability from impairment of ventilatory capacity or recurrent chest illnesses should be regarded as complications, and not as essential features of chronic bronchitis, since it is important to recognize the disease before it has resulted in disability. Only prospective studies can determine the prognosis of the suggested grades of bronchitis in respect to the development of disability. The disabling form of the disease can be referred to as "chronic bronchitis with ventilatory impairment" and "chronic bronchitis with recurrent exacerbations," and may be graded according to the severity of the impairment and the frequency of exacerbations. Disability appears to be a less frequent consequence of chronic bronchitis in men than in women (after authors' summary).—E. A. Riley

The Specificity of the Tuberculin Reaction in Man in Great Britain. T. M. Pollock*, I. Sutherland, P. D'Arcy Hart, A. Harries, J. Leach, K. Mercer, C. Miller, and B. Simonds. *Tubercle*, October, 1959, 40: 336–354. (*Medical Research Council, London, England)

Between 1954 and 1956, a total of 7,646 Royal Air Force recruits were tested with a series of increasing doses of Old Tuberculin. In 6,110 participants, the doses were 0.3, 1, and 3 tuberculin units (TU), followed—in those negative to 3 TU—by 10, 30, and 100 TU. In the other 1,536 participants, the doses were 1 and 3 TU, followed—in those negative to 3 TU—by 10, 30, 100, and 1,000 TU. The main purpose of the inquiry was to study the possibility that the positive reactions to a high dose of tuberculin, among persons with negative reactions to a low dose, had been produced by an agent other than the tubercle bacillus. The approach adopted was an extension of that previously used by Palmer and his colleagues in the U. S. A. when studying similar material in nurses. A detailed study on these lines showed, however, no association with contact history for any dose of tuberculin greater than 1 TU; thus, if the arguments used are valid, nonspecificity in Britain apparently begins at 1 TU of OT. This concept is clinically difficult to accept, and the approach based on contact history has therefore been questioned.

The frequency distribution of the tuberculin reactions by diameter of induration showed that there was a better differentiation between negative and positive reactions with 3 TU than with 1 or 0.3 TU, and for those reporting contact than for those reporting no contact. The absence of any change in the type of distribution with increasing dose suggests that the reactions to a high dose of tuberculin did not differ essentially from reactions to a low dose. The average diameter of the positive reactions to 0.3, 1, and 3 TU was greatest for those reporting close contact and least for those reporting no contact. Thus the intensity, as well as the frequency, of positive reactions was associated with contact history.

The general validity of the epidemiologic-statistical arguments used by Palmer has been critically examined in the light of the present findings. It has been concluded that these arguments are inadequate to demonstrate the occurrence, in man in Britain, of tuberculin sensitivity which is associated with reactions only to a strong dose of tuberculin (of the order of 100 TU), and which is not due to tuberculous infection (though such sensitivity may well exist in other parts of the world, as claimed by Palmer). So far, on the evidence available, weak degrees of tuberculin sensitivity in man in Britain appear to be explicable on the basis of tuberculous infection. Immunologic studies using tuberculins prepared from different mycobacteria probably represent the best way to determine, in Britain and elsewhere, whether tuberculin sensitivity in man occurs to an appreciable extent as cross reactions to agents other than *M. tuberculosis*.—M. J. Small

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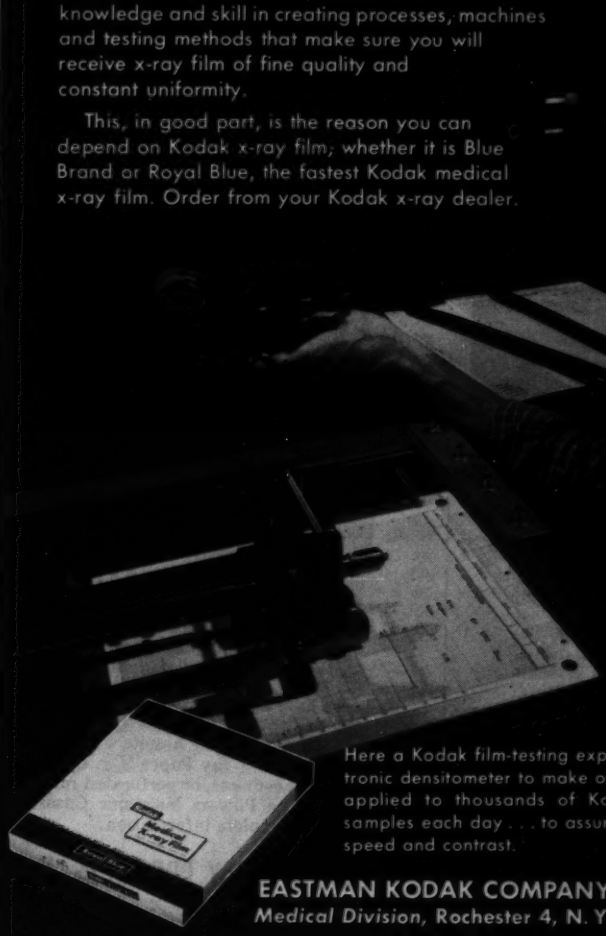

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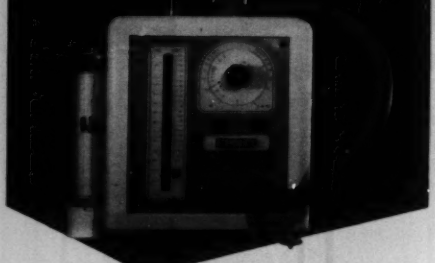

The Timed Vital Capacity is expressed as % of measured V.C. during an adjustable time (0.5-1.0 or 1.5 sec. also available 1,2,3 sec.) The patient makes a forced expiration into the PULMOMETER. Two pointers move at the same time over a lighted scale. One indicates the V.C., the other stops automatically after the set time and gives the M.B.C. The PULMOMETER is easy to operate and inexpensive. Tests are easy to repeat and yield direct readings without calculation. Available with or without recorder for permanent record.

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AMERICAN REVIEW OF RESPIRATORY DISEASES

Audience Profile

An analysis based on every tenth name of our United States subscription list checked against the *AMA 1958 Directory* to insure proper *geographical coverage*

Total Circulation	8,128
United States	4,651
Canada	250
Foreign and Miscellaneous	3,227

PHYSICIANS

SPECIALTY

	No.	%
No specialty	50	11.46
Starred pulmonary specialist	84	19.27
Pulmonary specialist	24	5.50
Starred internist	85	19.49
Starred surgeon	31	7.10
Surgeon	3	.68
Starred thoracic surgeon	27	6.19
Starred radiologist	7	1.60
Starred public-health specialist	5	1.14
Starred pathologist	3	.68
Starred pediatrician	3	.68
Starred otologist	2	.45
Starred and unstarred specialists in allergy, bacteriology, gastroenterology, hospital administration, industrial medicine, OALR, OBG, orthopedic surgery, physical medicine—one each	9	2.06
No information	17	3.89
	350	80.19
Institutional subscribers	86	19.72
	436	99.91

MAJOR PROFESSIONAL INTEREST

	No.	%
General private practice	22	5.04
Primary interest in internal medicine and pulmonary diseases	170	38.99
GP with interest in pulmonary diseases	24	5.50
Physician in advanced training	17	3.89
Full-time hospital staff	76	17.43
Full-time medical-school staff	7	1.60
Hospital administration	2	.45
Special research	1	.22
General public-health practice	10	2.29
Retired	3	.68
Not in practice	1	.22
No information	17	3.89
	350	80.19
Institutional subscribers	86	19.72
	436	99.91

AGE OF PHYSICIAN

	No.	%
No information	17	3.89
No age given	1	.22
30–34	10	2.29
35–39	55	12.61
40–44	58	13.30
45–49	50	11.46
50–54	51	11.69
55–59	37	8.48
60–64	35	8.02
65 and over	36	8.25
	350	80.21
Institutional subscribers	86	19.72
	436	99.93

POPULATION

	No.	%
Under 10,000	56	12.84
10–25,000	39	8.94
25–50,000	44	10.10
50–100,000	38	8.71
100–200,000	32	7.33
200–500,000	48	11.00
500–1,000,000	39	8.94
Over 1,000,000	54	12.38
	350	80.24
Institutional subscribers	86	19.72
	436	99.96

BREAKDOWN OF INSTITUTIONAL SUBSCRIPTIONS

Federal Hospital	General Hospital	Special Hospital	Laboratory	Medical Schools	College University	Society Library	Population
3	2	5	2	0	1	0	Under 10,000
3	2	1	0	0	1	0	10–25,000
0	2	4	0	3	2	1	25–50,000
1	1	1	0	1	2	2	50–100,000
2	0	1	1	0	0	2	100–200,000
3	6	0	0	0	1	4	200–500,000
4	3	2	0	0	1	0	500–1,000,000
2	4	1	1	2	0	6	Over 1,000,000
18 4.12%	20 4.58%	15 3.44%	4 .91%	6 1.37%	8 1.82%	15 3.44%	86 19.72%

Percentages figured only to second decimal point

See inside front cover for subscription rate

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The Automatic TB Case-Finding Device for the Heaf TUBERCULIN TEST

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ADVANTAGES...

- Four (4) times faster than Mantoux.
- Faster and more reliable than Patch test.
- Performs up to 400 tests per hour.
- Detects reactors to 5 TU Mantoux and some 100 TU reactors.
- No dressing required.
- Accurate interpretation, without measurement. Averages 250 readings per hour.
- Each test is uniform—puncture of 1 mm. depth and needle withdrawal is automatic.
- No special skill required.
- Painless. Ideal for testing children.
- Eliminates hazardous and uncertain flame sterilization.
- Disposable needle cartridges ELIMINATE CROSS-INFECTION.
- Low cost STERNEEDLE cartridges may be resterilized.

Procedure for STERNEEDLE TUBERCULIN TEST:

Top, left...Slip needle cartridge on gun with plastic applicator. Remove applicator.

Top, right...Place a drop of tuberculin PPD on cleansed forearm.

Bottom, left...Place gun on drop of tuberculin PPD. Pressure and release of handle automatically triggers and retracts the needles.

Bottom, right Disposable needle cartridges and applicators may be washed and sterilized for reuse, if desired.

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